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Research Article

Drug-Related Problems in Type 2 Diabetes Patients with Acute Hyperglycemia

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Abstract

Patients with type 2 diabetes mellitus (T2DM) and acute hyperglycemia are at risk of drug- related problem (DRPs) due to unstable haemodynamic system and multiple comorbidities that require them to take multiple medications. This retrospective study was conducted to assess the types of DRPs. The assessment of DRPs was based on Pharmaceutical Network Care Europe (PCNE) tool V5.01. Among the 239 cases of acute hyperglycemia, a total of 466 DRPs had been identified, an average of 2.66 ± 2.058 DRPs per patient. The most common DRPs encountered were potential drug-drug interactions (48.9%), drug choice problem (41.5%), dosing problem (28.2%) and adverse reaction (26.9%). Drug/dose selection (24.3%), others (13.8%) and patient/psychological factors (10.6%) were the most common causes contributing to DRPs. Therefore, early identification of risk of DRPs among T2DM patients with acute hyperglycemia may enhance the pharmacological treatment and reduce risk of mortality and morbidity.

Keywords: *Type 2 Diabetes Mellitus (T2DM); Drug-Related Problem (DRPs); Pharmaceutical Network Care Europe (PCNE)*

Introduction

Uncompensated diabetes mellitus manifested as acute hyperglycemia consist of diabetic ketoacidosis (DKA), hyperglycemic hyperosmolar state (HHS) and hyperglycemia without HHS and DKA [1] that commonly occurred in poorly control blood glucose level among diabetic patients [2]. Patients are often hospitalized due to acute hyperglycemia which eventually causes morbidity and mortality if left untreated [3]. Despite major advances in their management, mortality rate was reported to be 5 - 20% in HHS and typically observed in elderly with T2DM while in DKA, mortality rate encountered for < 2% of T2DM patients [1].

DKA has always been described to be closely linked to type 1 diabetes (T1DM) but recently, DKA is preferred to be associated with T2DM [4]. Study conducted by Seth., *et al.* revealed that among 60 patients presented to emergency with DKA, 20% have T1DM while 80% have T2DM showing prevalence of T2DM is higher than T1DM [5]. Meanwhile, HHS usually develops slower than DKA and higher prevalence can be seen in T2DM, involving 7 - 17% of the patients [6]. DKA, HHS and hyperglycemic without DKA and HHS can establish in the presence of infection as predominant factor, followed by non-compliance to antidiabetic therapy and used of certain medication such as corticosteroid and antipsychotic [7].

Acute hyperglycemia could lead to numerous severe complications due to unstable haemodynamic system, and thus critical care of hospitalized T2DM patient is required [1]. However, frequency of drug-related problems (DRPs) remain persistently high in clinical prac-

tice with consequence including hospital admission, prolonged hospital stay and death [8]. DRPs generated during hospitalization could be due to unnecessary or contraindicated drugs, overdosing, or excessive duration of treatments [9]. DRP can be described as "an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes" (PCNE, 2006). According to Singh Gangwar., *et al.* high prevalence DRPs has been observed in patients with T2DM especially in aging population due to the presence of multiple comorbidities which require polypharmacy [10]. DRP in acute hyperglycemia not only associated with significant morbidity and mortality, it also brings substantial economic burden [8]. Nevertheless, DRPs can be avoided and yet preventable by enhancing optimization of pharmacotherapy treatment and therefore able to curb unnecessary iatrogenic risk [11].

The identification, resolution and prevention of DRPs have been stated to be fundamental to the process of pharmaceutical care in order to achieve improved therapeutic and eventually quality of life [12]. Having said that, since acute hyperglycemia presented with unstable haemodynamic system, inappropriate medication may lead to DRPs. Therefore, this study sought to assess DRPs in T2DM patients with acute hyperglycemia.

Methodology

Study population and sampling frame

This study involved hospitalized type 2 diabetes mellitus (T2DM) patients with acute hyperglycemia. Registered patients from 2007 until 2016 had been identified from Medical Record Unit, UMMC and all of the patients which fulfilled the requirement of E11 in International Classification of Disease Tenth Revision (ICD-10) were selected. The estimated sample size was calculated using Epi Info Program Version 7.0 (CDC, Clifton Rd. Atlanta, USA). The expected proportion of T2DM patients was 22.9% [13]. Level of significant was set to 0.05 and desired power of study (1-β) was 80%. Meanwhile, confidence interval was assumed to be 0.05 with 95% confidence level. Thus, the calculated minimum sample size was 142 patients.

Study design and procedure

This retrospective study was conducted in University Malaya Medical Centre (UMMC) with approval from Medical Ethic Committee of University Malaya Medical Centre (UMMC) (Medical Ethic Committee Number: 201510-1767). A total of 1200 registration numbers from 2007 until 2016 which fulfilled ICD-10 (code E11) had been generated using Hospital Information System (HIS). There were 450 medical records in the form of e-document and hardcopy successfully retrieved from Medical Record Unit (MRU). However, only 201 patients fulfilled the inclusion and exclusion criteria and were included in this study. 239 cases of acute hyperglycemia had been identified among these 201. Cases were recorded based on number of patients' admission. Each patient can be presented with at least one case and at most 3 cases.

Inclusion criteria

1. Adult type 2 diabetes mellitus (T2DM) patients who are equal or more than 18 years old.
2. T2DM patients with acute hyperglycemia with blood glucose level exceeding 15 mmol/L upon hospital admission.

Exclusion criteria

1. Patients with human immunodeficiency virus (HIV) and cancer.
2. Patients with other types of diabetes mellitus.

Data collection form

Data collection forms were used to collect all the related information from eligible patients which included demographic criteria of patients consist of age, sex, ethnicity, weight, height, body mass index (BMI), smoking and alcohol consumption status and duration of patients diagnosed to have type 2 diabetes mellitus (T2DM). Clinical characteristics of patients were also included such as co-morbidities that showed existing other health problems in patients, concomitant medications showing the administration of multiple drugs for multiple comorbidities, laboratory findings, type of acute hyperglycemia, A1c level, admission glucose and type of insulin regimen used among T2DM patients with acute hyperglycemia.

Age, gender, duration of having diabetes mellitus, type of acute hyperglycemia, comorbidities, concurrent medication, A1c level, admission glucose and type of insulin regimen were the parameters used to associate with occurrence of DRPs.

Terms	Definition
Comorbidities	Co-occurrence of two or more health problems included diseases, disorders, conditions and illnesses [14].
Polypharmacy	The administration of 5 or more type of medications [11].
Elderly	65 years old and above [15].
BMI range (kg/m^2)	Below 18.5 (Underweight); 18.5-24.9 (Normal or Healthy Weight); 25.0-29.9 (Overweight); 30.0 and above (Obese) [16].
Admission glucose	The level of admission glucose was set at 33.0 mmol/L as cut off point for hyperosmolar hyperglycemic syndrome (HHS) due to most HHS have the highest plasma glucose compared to diabetic ketoacidosis (DKA) [17].
A1c level	Level of A1c was set up to <8% to indicate controlled blood sugar and ≥ 8% to indicate poor glycemic control. 8% was less stringent A1c level that applied due to advance in microvascular and macrovascular complication, extensive comorbidities and long-term diabetes in whom general A1c target are difficult to attain [18].
Acute infection	Acute infection occurred in short period of time and cause release of systemic inflammatory response that may elevate plasma sugar level [19].
Acute cardiovascular disease	Acute coronary syndrome or acute cardiovascular disease such as acute myocardial infarction, unstable angina and acute ischemic stroke may lead to hyperglycemia [19].

Table 1: *Definition of term.*

Assessment of drug-related problems (DRPs)

PCNE Classification Version 5.01 was used as a tool to assess factors associated with DRPs in T2DM patients throughout this study. This tool is structured with 6 primary domains for problems, 6 primary domains for causes and 5 primary domains for intervention. On a more detailed level there are 21 grouped sub domains for problems, 33 grouped sub domains for causes and 17 grouped sub domains for interventions. However, intervention domain and sub domain were excluded from this tool as study was focusing on factors associated with DRPs in T2DM patients (PCNE, 2006). All the filled data collection forms were screened and analyzed in order to determine the occurrence of DRPs among T2DM patients along with their admission in the wards. Classifications of DRPs were done by referring to generated DRPs reference tool (Appendix 2) in addition to MIMS 139th Edition, British National Formulary (BNF) 67 and Drug Information Handbook 24th Edition.

Statistical technique

All the collected data were loaded into IBM Statistical Package for the Social Sciences (SPSS) Software Version 21.0 and analyzed according to the objectives of the study. The data were presented as categorical or continuous. Normality test was done on continuous data to determine the normality of the distribution. The normality of the data was also inspected via visualization by histogram, normal Q-Q plot as well as boxplot. The result for Shapiro-Wilk test was presented as skewness and kurtosis and expressed in mean ± standard deviation. Nominal data was presented as frequency and percentage (%). In addition, Chi-square test was used to analyze significant association between categorical data. Result from this test were presented as frequency, percentage (%) and p-value where $p < 0.05$ showed significant association between two categorical variables.

Results

Demographic characteristics of patients

A total of 239 cases of acute hyperglycemia had been identified involving 201 patients with type 2 diabetes mellitus (T2DM). One patient may be presented with one or more acute hyperglycemic cases which required hospitalization. The details of the demographic characteristics of the patients are presented in table 2.

Characteristics		Frequency	Percentage (%)
Ethnicity	Malay	81	40.3
	Chinese	31	15.4
	Indians	81	40.3
	Others	8	4.0
Gender	Male	94	46.8
	Female	107	53.2
Age category of patients	18 - 40	11	5.5
	41 - 54	52	25.9
	55 - 64	66	32.8
	65 and above	72	35.8
BMI of patients (kg/m^2)	Below 18.5	4	2.0
	18.5 - 24.9	22	10.9
	25.0 - 29.9	10	5.0
	30.0 kg above	17	8.5
	Unknown	148	73.6
Smoking history	Yes	24	11.9
	No	102	50.7
	Ex-smoker	18	9.0
	Unknown	57	28.4
Drink alcohol	Yes	17	8.5
	No	126	62.7
	Unknown	58	28.9

Table 2: *Demographic characteristics of patients (n = 201).*

Result showed that Malay (40.3%) and Indians (40.3%) were the two highest population admitted with acute hyperglycemia followed by Chinese (15.4%). Others ethnic (Non-Malaysian) represented as the minority of the patients admitted to University Malaya Medical Centre (UMMC) due to acute hyperglycemia. Of the total 201 T2DM patients with acute hyperglycemia, female (53.2%) was frequently observed to have acute hyperglycemia as compared to male (46.8%). Majority of the patients were 65 years and above with mean age 60.78 ± 12.204 years old. Shapiro-Wilk test ($p > 0.05$) and visual inspection of histogram, Q-Q plot and boxplot showed age of the patients were normally distributed among the ethnicity with significant value $p = 0.311$, skewness of 0.266 ± 0.172 and kurtosis value of 0.257 ± 0.341. Less than 30% of body mass index (BMI) was retrievable in this study with majority of patients were having normal BMI (18.5 - 24.9 kg/m^2). Meanwhile, 71.6% and 71.2% out of 201 patients' data regarding smoking history and alcohol consumption, respectively were available.

Clinical characteristics of patients

Clinical characteristics of the patients are shown in table 3. There was less than 40% data regarding duration of having T2DM unable to be retrieved. Most of T2DM patients with acute hyperglycemia were identified to be diagnosed with diabetes for less than 5 years and 10 to 20 years accounting for 19.4% for each category of duration.

Characteristics	N		Frequency	Percentage (%)
Duration of having T2DM	201	Less than 5 years	39	19.4
		5 - 10 years	21	10.4
		10 - 20 years	39	19.4
		More than 20 years	28	13.9
		Unknown	74	36.8
Type of acute hyperglycemia[b]	239	Diabetic ketoacidosis (DKA)	39	16.3
		Hyperosmolar hyperglycemic	66	28.0
		syndrome (HHS)		
		Hyperglycemia without DKA/HHS	133	55.6
Admission glucose[b]	239	< 33.0 mmol/L	173	72.4
		≥ 33.0 mmol/L	66	27.6
A1c level[b]	239	< 8%	22	9.2
		≥ 8%	131	54.8
		Unknown	86	36.0
Reason for admission[b]	239	Acute infection	86	36.0
		Acute cardiovascular disease	45	18.8
		Non-compliance	52	21.8
		Use of steroid	2	0.8
		Others	54	22.6
Comorbidities[∂]	201	Ischemic Heart Disease	69	34.3
		Congestive Heart Failure	11	5.4
		Hypertension	156	79.1
		Stroke	29	14.9
		Dyslipidemia	50	24.9
		Chronic Kidney Disease	50	24.9

Number of comorbidities[∂]	201	No comorbidity	12	6.0
		One	42	20.9
		Two	50	24.9
		Three	49	24.4
		Four	30	14.9
		Five	13	6.5
		Six	3	1.5
		Seven	2	1.0
Polypharmacy	201	Yes	159	79.1
		No	42	20.9

Table 3: *Clinical characteristic of patients.*

[b]: One patient may have more than one admissions.

[∂]: One patient may have more than one comorbidities.

Majority of T2DM patients were presented with hyperglycemia without diabetic ketoacidosis (DKA)/hyperosmolar hyperglycemic syndrome (HHS) (55.6%), followed by HHS, accounting for 28% of admissions and DKA (16.3%).

More than 50% of admissions, patients were admitted with A1c level more or equal to 8%. As A1c was not normally distributed, data was presented as mean ± standard deviation by which the overall mean was 11.29% ± 2.90% with mean of admission glucose 27.38 mmol/L ± 11.26 mmol/L.

Out of 201 patients, majority of T2DM patients have hypertension (79.1%), ischemic heart disease (34.3%) and chronic kidney disease ranging from mild to end stage renal failure (25.4%) as the top three leading comorbidities among T2DM patients. Some comorbidities such as arrhythmias, myocardial infarction, liver impairment, obesity, thyrotoxicosis, osteoarthritis, rheumatoid arthritis, benign prostatic hyperplasia (BPH), systemic lupus erythematosus (SLE) as well as gout occurred in less than 5%. Majority of T2DM patients were presented with at least two comorbidities whilst only twelve patients (6%) were presented without any comorbidities. Polypharmacy was observed in more than 30% of 201 T2DM patients with acute hyperglycemia.

Drug-related problems (DRPs)

A total number of 466 DRPs that occurred prior and during admission of patientin the ward were identified among T2DM patients with acute hyperglycemia. The mean number of DRPs was 2.66 ± 2.058 per patient with the number of DRPs range from 0 to 10. A total of 90.6% of 201 patients were identified to have at least one DRP. The top incidence of DRPs was 'Interaction' followed by 'Drug choice problem', 'Dosing problem', 'Drug use problem', 'Adverse reaction' and the least DRPs occurred was 'Others'. The details of each domain of the DRPs that occurred among T2DM patients with acute hyperglycemia were presented in table 4.

Code	The problem	Number of problem (%)
P1	**Adverse reaction**	**64 (26.9)**
P1.1	Side effect (non-allergy)[b]	58 (24.4)
P1.2	Side effect (allergy)	1 (0.4)
P1.3	Toxic effect	5 (2.1)
P2	**Drug choice problem**	**106 (41.5)**

P2.1	Inappropriate drug (not most appropriate for indication)	37 (14.5)
P2.2	Inappropriate drug form (not most appropriate for indication)	2 (0.8)
P2.3	Inappropriate duplication of therapeutic group or active ingredient	12 (4.7)
P2.4	Contraindication for drug	5 (2.0)
P2.5	No clear indication for drug use	11 (4.3)
P2.6	No drug prescribed but clear indication	39 (15.2)
P3	**Dosing problems**	**72 (28.2)**
P3.1	Drug dose too low or dosage regime not frequent enough	23 (9.0)
P3.2	Drug dose too high or dosage regime too frequent	43 (16.8)
P3.3	Duration of treatment too short	3 (1.2)
P3.4	Duration of treatment too long	3 (1.2)
P4	**Drug use problem**	**66 (25.8)**
P4.1	Drug not taken/administered at all[b]	66 (25.8)
P5	**Interaction**	**125 (48.9)**
P5.1	Potential interaction	125 (48.9)
P6	**Others**	**33 (13.0)**
P6.1	Patients dissatisfied with therapy despite taking drug(s) correctly	4 (1.6)
P6.2	Insufficient awareness of health and disease	16 (6.3)
P6.3	Unclear complaint	3 (1.2)
P6.4	Therapy failure	10 (3.9)

Table 4: *Classification of drug-related problems (DRPs) (n = 466).*

One patient may be presented with one or more DRPs. DRPs with frequency 1 and more were included.

[b]DRPs that occurred prior to admission would be taken into consideration.

Meanwhile, 128 causes of DRPs were identified in this population study which 'Drug/dose selection' was the major cause of DRPs. It was found in 58 cases of T2DM with acute hyperglycemia. This was followed by 'Others', 'Patient/psychological factors' and 'Drug use processes'. However, 'Logistic' was not the cause of DRPs. The description regarding the causes of DRPs is shown in table 5.

Code	The cause	Number of cause (%)
C1	**Drug/dose selection**	**58 (24.3)**
C1.1	Inappropriate drug collection	14 (5.9)
C1.2	Inappropriate dosage selection	1 (0.4)
C1.4	Pharmacokinetic problems, including aging/deterioration in organ function and interaction	20 (8.4)
C1.5	Synergistic/preventive drug required and not given	17 (7.1)
C1.6	Deterioration/improvement of disease state	2 (0.8)
C1.8	Manifest side effect, no other cause	4 (1.7)
C2	**Drug use process**	**12 (5)**
C2.2	Drug underused/under-administered[+]	9 (3.8)
C2.3	Drug overused/over administered	1 (0.4)
C2.6	Patient unable to use drug/form as directed[+]	1 (0.4)

C4	**Patients/Psychological**	**25 (10.6)**
C4.1	Patient forget to use/take drug*	10 (4.2)
C4.2	Patient has concerns with drugs*	4 (1.7)
C4.3	Patent suspects side-effect	3 (1.3)
C4.4	Patient unwilling to carry financial costs	1 (0.4)
C4.7	Patient unwilling to adapt life-style*	7 (3.0)
C6	**Others**	**33 (13.8)**
C6.1	Other cause; specify	11 (4.6)
C6.2	No obvious cause	22 (9.2)

Table 5: *Classification of cause of drug-related problems (n = 128)*

Causes of DRPs with frequency more than 1 were included.

**: Causes of DRPs occurred prior to admission would be taken into consideration.*

On the other hand, 520 drugs were identified to cause DRPs in all 239 cases of T2DM patients with acute hyperglycemia whereby one drug may cause more than one DRP for each case. Figure 1 shows the different classes of medications that contribute to the occurrence of DRPs.

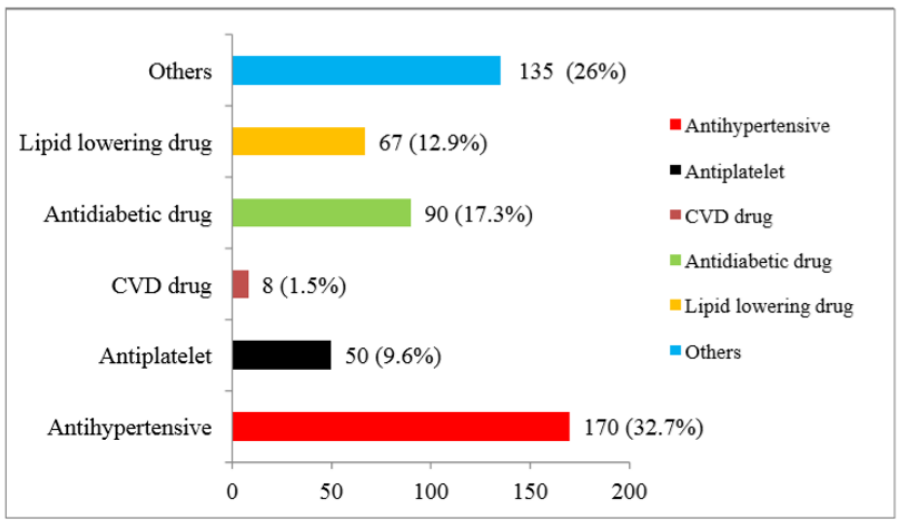

Figure 1: *Classes of medications that cause DRPs (n = 520).*

The most likely drug class that caused incidents of DRPs were antihypertensive drugs mainly beta-blocker (12.4%), calcium channel blocker (9%), loop diuretics (6.5%) and ACE I (4.8%). Other drugs categorized under antihypertensive had fewer contributions to DRPs which only found in less than 5 cases.

Besides, antidiabetic drug such as insulin and oral hypoglycemic agent (OHA) were observed to cause 5.4% and 11.3% of DRPs, respectively. Meanwhile, simvastatin (12.3%) was the major drug in lipid lowering group contributed to DRPs. There were only 3 cases with DRPs observed with administration of atorvastatin and fenofibrate.

Antiplatelet that contributed to DRPs incidents was clopidogrel (5.6%) followed by aspirin (2.5%) while heparin, ticlopidine, fondaparinux and enoxaparin contributed to 1.5% of DRPs in total. Digoxin, warfarin and ivabradine were cardiovascular (CVD) drug that accounted for 1.5% of total drug prescribed causing the DRPs. Apart from that, drugs that categorized under 'Other medication' that commonly involve in DRPs issues were proton pump inhibitor (PPI), potassium chloride and prednisolone.

On the other hand, out of 520 drugs contributed to occurrence of DRPs, 125 drugs were identified to be involved in potential interactions. The highest interaction can be seen with co-administration of beta-blocker and insulin (28.8%). Particularly, metoprolol was the frequent beta-blocker prescribed in 239 admissions. It was followed by interaction between calcium channel blocker (CCB) mainly amlodipine with simvastatin (25.6%)and furosemide with insulin (15.2%). The detail of the result is presented in figure 2.

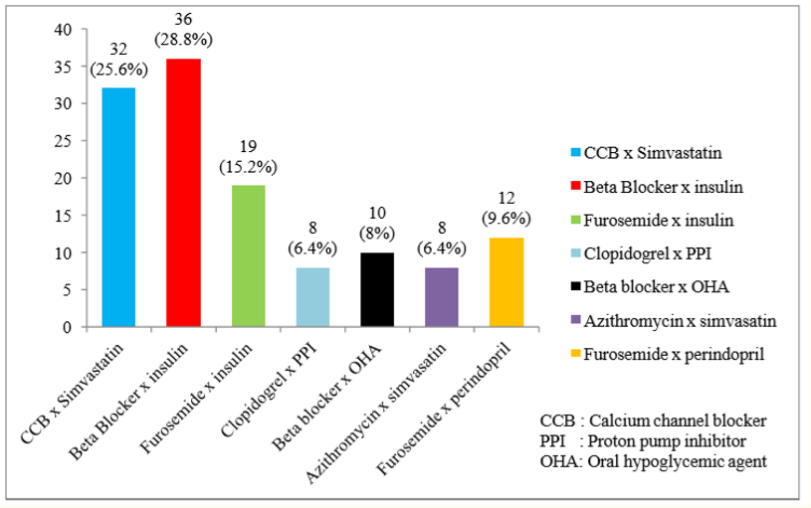

Figure 2: *Medications with potential drug-drug interactions (n = 125).*

Discussion

Drug-related problems (DRPs)

PCNE classification was used to reflect and identify all the DRPs incidents throughout ward stay and prior to admission in this study. In average each patient had 2.66 ± 2.058 DRPs with more than 90% of total subjects had at least one DRP. This finding agreed with previous study reporting approximately 91% of total subjects having at least one DRP for each patient [20]. However, when comparing with a recent study, mean of DRPs identified was 1.94 ± 1.10 per patients although the identification of DRPs was analyzed by the same PCNE tool [21]. This difference might be associated with widely use of insulin as the main treatment in acute hyperglycemia which frequently caused DRPs. Consequently, this can be contributed to the increment of the occurrence of DRPs per patients.

The top four frequent DRPs occurred in this population were 'Interaction', 'Drug choice problem', 'Dosing problem' and 'Drug use problem' (Table 4). In contrast, previous study on 73 patients identified adverse reaction (24%) was the common DRPs, followed by drug use problem (14%) and dosing problem (10%) [22]. The higher percentage of DRPs in current study as compared to study conducted by Granas., *et al.* may be related to different number of patients involved in each study.

Interaction

No 'Manifest interaction' was identified in any cases involving T2DM with acute hyperglycemia. Potential drugs interactions could be observed in 239 admissions comprising of 62% of total cases collected. Figure 2 visualize the medications contributed to occurrence of potential interactions in this study. Current study revealed concomitant use of beta blocker with insulin was the most common potential interaction. This finding was not consistent with the result in previous studies suggested that simvastatin and amlodipine was the highest contributor to potential drug interaction [21]. Meanwhile, another study done on the T2DM patients with hypertension proposed that most potential interaction occurred with concomitant use of clopidogrel with aspirin which can be observed in 25 patients [23]. The variation of finding in current and previous studies may be due to difference in target population using different medications as main treatment. A study analyzed that risk of developing diabetes was 28% greater in patients taking beta blocker compared to those who do not take beta-blocker. This explained beta blocker may decrease level of insulin and may worsen the glucose control [24].

Another significant potential interaction implicated in this study was calcium- channel blocker (CCB) which was amlodipine and simvastatin which was also reported in 2 studies on T2DM patients with dyslipidemia and hypertension [21,23]. By 2011, Food and Drug Administration (FDA) recommended 20 mg as dose limitation in prescribing simvastatin concurrently with amlodipine due to increase risk of myopathy and rhabdomyolysis [25]. However, 16% of total acute hyperglycemic cases among T2DM patients were observed to concomitantly receive simvastatin 40 mg and amlodipine. Amlodipine may increase simvastatin level when they were concomitantly administered. It was proven by recent study on pharmacokinetic of both drugs that co-administration of amlodipine 10mg and simvastatin 40 mg may increase bioavailability of simvastatin by 46% with 13% reduction in simvastatin clearance [26].

The potential drug interaction identified in this study was based on clinical evidence yet some drugs are still allowed in clinical practice. Manifestation of interaction will take some time to develop. Thus, close monitoring is important to identify any side effect or toxicity that is caused by drug-drug interactions.

Drug choice problems

'No drug prescribed despite clear indication' occurred in 39 out of 239 cases of acute hyperglycemia. Common drugs involved in this DRP were simvastatin and aspirin which occurred in 8% of admissions for each drugs. Both of the drugs were observed not being prescribed in 20 cases which were required as secondary prevention in ischemic heart disease (IHD) and stroke. This finding was in line with study by van Roozendaal which encountered similar drugs that involve in drug choice problem, 61% and 48% were not prescribed with antiplatelet and simvastatin despite the drugs were required [27]. Similar finding was also reported by another study that the need for additional therapy such as antiplatelet was among the common DRPs occurredin T2DM patients [28]. Study found that use of statin would result in 25% reduction in risk of recurrent stroke and 20% reduction for all of other vascular disease [29]. Meanwhile in elderly, aspirin was found to be beneficial in prevention of IHD as well as stroke even though similar benefit was found in other alternative antiplatelet. Nevertheless, high compliance to aspirin was the main concern of its choice [30].

Other drug involved in this DRP were metformin. Metformin was observed to be prescribed in 5 cases of patients with liver cirrhosis. This inappropriate prescription might affect pharmacokinetic of metformin as it was extensively metabolized by hepatic enzyme. Potassium chloride (KCl) was also identified to cause DRP. Inappropriateness of KCl observed as it being prescribed in patients with normal potassium level. Hypokalemia was a significant side effect of insulin but the occurrence in this study was less than 1%. Thus, close monitoring of potassium level is very crucial in patients receiving insulin due to hypokalemia event as adverse effect of insulin rather than prescribing additional drug into patients' medications list.

Dosing problems

Excessive drug dose or frequent regimen was the most frequent dosing problems, accounted for nearly 17% of total DRPs. Underdose was also observed as significant dosing problem. Study conducted by Huri and Wee reported the lower occurrence of excessive administration of drugs as compared to current study whereby 11.3% of T2DM patients with hypertension received higher dose of medication [23]. This DRP was probably related to chronic kidney disease which commonly occurred among study population which might affect the pharmacokinetic and pharmacodynamics of the drugs. Thus, critical assessment for renal function is required among T2DM patients with acute hyperglycemia.

The most implicated drug was perindopril. Despite perindopril was proven to reduce kidney disease progression, study by James., *et al.* otherwise found that angiotensin- converting-enzyme inhibitors (ACE I) was the best antihypertensive agents for non- diabetic kidney impairment [31]. This was in line with another study that show perindopril exert significant adverse reaction in Chronic Kidney Disease (CKD) stage 3 and above among T2DM patients [32]. Thus, drugs such as perindopril can still be used in CKD but dosage should be reduced proportionally to the predicted kidney creatinine clearance [33].

Therefore, effort should be made to assess the kidney profile of patients before dispensing any drug that is highly excreted by kidney among T2DM patients with CKDin order to reduce dosing problem.

Adverse reaction

Almost 25% of occurrence of DRPs was associated with side effect (non-allergy). The highest side effect observed in this population was hypoglycemia which is associated with the administration of OHA and insulin. This finding was supported by previous study which identified antidiabetic drug as common drug associated with adverse events [22]. Administration of sliding-scale insulin was the common cause of hypoglycemia in current study. Study by Huri., *et al.* on comparison of sliding-scale and basal bolus insulin to glycemic control revealed that sliding-scale significantly caused hypoglycemia compared to basal-bolus regimen ($p = 0.005$) [34]. Most studies proved sliding-scale insulin may cause glucose variability as the administration of insulin by this regimen depends on glucose level instead of body weight of patients [35]. Therefore, strict implementation should be done in clinical setting to reduce the use of sliding-scale insulin which can potentially cause hypoglycemia, thus reduce the duration of ward stay.

Besides, the adverse reaction prior to admission was also taken into consideration which in this study, uptake of steroid contributed to 2 occurrences of side effects (non- allergy) related to hyperglycemia. Previous study reported 40% of acute hyperglycemic admissions were due to exacerbation of steroid as this medication could increase insulin resistance [36]. In spite of steroid-induced hyperglycemia being less significant in this study due to very small frequency, caution is still required and thus,this DRP can be preventable.

Causes of DRPs

Result from this study revealed that "Drug/dose selection" was the main contributor to the occurrence of DRPs in T2DM patients with acute hyperglycemia. Pharmacokinetic problem (C1.4) was identified to cause more than 8% of acute hyperglycemic cases. Aging was characterized to have alteration in physiological, pharmacokinetic and pharmacodynamics response which makes elderly more vulnerable to adverse reaction [37]. In contrast, this study found that there was no significant association between age and occurrence of DRPs ($p = 0.388$) which was in line with previous study conducted by Granas and colleague ($p = 0.418$) [22]. Aside from that, 7% of DRPs were caused by unadministered of synergistic/preventive drug despite it was required. As mention above, simvastatin and aspirin were the common drugs that were not prescribed as stroke or IHD prevention which leads to DRP P2.6.

Meanwhile, current finding showed that 'drug use problem' was commonly caused by 'patients' psychological factors' such as forget to take drugs and 'drug use process' such as underuse of medications. Furthermore, "no obvious cause" (C6.2) were identified in 9% of acute

hyperglycemic cases which could explain "Unclear complaint" that had been observed in this study. The number of causes identified in this study were much lower as compared to others studies which identified more than 300 causes of DRPs [23,38]. The huge difference was probably due to most of the problems identified was matched with one related cause rather than several causes and limited availability of data regarding the cause of DRPs.

Conclusion

'Potential interaction' was the highest DRPs identified in T2DM patients with acute hyperglycemia with most implicated drugs were insulin, beta-blocker, simvastatin and calcium-channel blocker (mainly amlodipine). Other DRPs observed in the study were drug choice problem, dosing problem, adverse reaction, drug use problem and DRPs categorized under 'Others'. These DRPs were caused by drug/dose selection, patients/psychological, drug use process and other cause that could not be clearly identified.

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