The Effect of Drug-Related Problems on Blood Glucose Level in the Treatment of Patients with Type 2 Diabetes Mellitus

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Abstract

AIM: The study aimed to investigate the effect of drug-related problems (DRPs) on changes in blood glucose level (BGL) in the treatment of type 2 diabetes mellitus (T2DM) patients.

METHODS: This three-month prospective cross-sectional study was conducted to patients of T2DM with complications hospitalised in Haji Adam Malik (HAM) Hospital, Medan, Indonesia period from July to October 2018. DRPs were identified and classified by using Cipolle DRP classification and trustable literature. The data obtained were analysed by Chi-Square test ($p < 0.05$ implied that there was a significant relationship).

RESULTS: This study involved 81 T2DM patients, 52 (64.2%) of the patients were male, and 29 (35.8%) of them were female. Most (30.9%) of patients were at the age of 51-60 years. Combination of rapid-acting and long-acting insulin was the most frequently provided antidiabetic drugs (69.1%). There were 68 DRPs experienced by 32 (39.5%) of the patients. Percentage of DRP experienced by the 32 patients by number: 1 DRP, 53.1; 2 DRPs, 28.1; 3 DRPs, 3.1; 4 DRPs, 3.1; 5 DRPs, 3.1; 7 DRPs, 9.3. This study showed that 27.2% and 12.3 % of the patients had hyperglycemia and hypoglycemia, respectively. There was no significant relationship between BGL and indication without drug therapy ($p = 0.064$), ineffective provided drug ($p = 0.079$), and there was a significant relationship between BGL and irrational dose ($p = 0.000$). Furthermore, there was a significant relationship between hypoglycemia and adverse drug reaction ($p = 0.000$).

CONCLUSION: DRPs are common among T2DM patients and still required the attention and appropriate actions of healthcare providers.

Introduction

Diabetes mellitus (DM) is a metabolic disease characterised by high BGLs in the body caused by defects in insulin secretion, insulin action, or both. In 2017, Indonesia was ranked as the 6th highest prevalence of diabetes in the world in which the number of people with diabetes mellitus reached 10.3 million and is expected to rise to 16.7 million in 2045 [1]. It was estimated 1 death every 6 to 10 seconds caused by its complications around the world [2]. Hyperglycemia that occurs, over time, can damage various body organs, especially the nerves and blood vessels. Macrovascular and microvascular complications can occur in patients with diabetes mellitus. Common developed macrovascular complications that occur in people with diabetes is coronary heart disease, blood vessel disease in the brain, and peripheral vascular disease [3].

The disease and its complications experienced by diabetes mellitus patients required polypharmacy (multiple drug therapy) which in turn can cause DRPs [4], that actually or potentially interfere with the desired outcome of therapy [5]. This condition can further worsen the patients' quality of life, increase their length of stay and treatment costs. On the other side, the limitation of health resources is a serious problem in the universal health coverage era. Facts indicated that the National Health Insurance has been facing financial difficulties to run the program [6], [7]. These problems should be responded and resolved.

Several studies on DRPs have been conducted by researchers applying different

classification methods. In 2018, a study performed in Tegal, Indonesia stated that drug dose and drug choice problems were the highest DRPs of the overall incidences [8]. Also, another study conducted in Medan proved that the most frequently occurred DRP was indication without therapy and there was no significant association between the patients' education and DRPs (p = 0.88) [9]. Research on DRPs is still limited in Indonesia.

The study aimed to investigate the effect of DRPs on changes of BGLs in the treatment of T2DM patients. This study focused on antidiabetic utilisation, identification and analysis of DRPs in the management of T2DM as well as the association between DRPs and changes of BGLs.

Methods

This prospective cross-sectional study was undertaken on T2DM inpatients admitted to HAM, Medan, Indonesia. In this study, the number of patients recruited as subjects was 81 hospitalised from July to October 2018. The patients diagnosed with T2DM with a complication, aged ≥ 18 years, received oral antidiabetics or insulin and other medicines (combination therapy) and have provided their consent were included in this study. Ethical clearance of this study was obtained from The Ethical Commission of Health Research, Faculty of Nursing, Universitas Sumatera Utara, Medan. Characteristics of patients, including gender, age, and co-morbidities, were recruited from their medical records. Drugs provided to the patients, important laboratory results and BGL as clinical outcome were also extracted from their medical records.

Characteristics of T2DM patients and drug utilisation were descriptively analysed. Incidence of DRPs in the management of T2DM was identified and analysed based on Cipolle DRP classification system that comprises indication without drug therapy, ineffective provided drug, too low doses, too high doses, drug interaction and adverse drug reaction [10]. The analysis of the occurred DRPs referred to trustable literatures including the authority on drug interactions, a sourcebook of adverse interactions, their mechanisms, Medscape Reference, IBM Micromedex Reference [11], [12], [13], [14] and guidelines for the management of T2DM [15], [16], [17], [18]. The BGLs of the T2DM patients were grouped into 3 categories that are normoglycemia (< 200 mg/dl), hyperglycemia (≥ 200 mg/dl), and hypoglycemia (< 70 mg/dl). The relationship between the occurred DRPs as an independent variable with BGL as a dependent variable was analysed by Chi-Square tests [19] in the program of Statistical Package for the Social Sciences (SPSS) version 25 (p < 0.05 is considered significant).

Results

During the study period, there were 81 patients fulfilled the inclusion criteria consisted of 64.2% male and 35.8% female. Table 1 shows the demographics of T2DM patients. Most (30.9%) of the patients were at the age of 51-60 years. The number of drugs given to the patients varies, ranging from 6 to 20 items. The most common complications or comorbidity experienced by the patients were; heart failure (11.8%) and hypertension (9.1%).

Table 1: Demographics of the T2DM patients (n = 81)

Characteristics	% of patients
Gender:	
Male	64.2
Female	35.8
Age:	
≤ 40	7.4
41-50	25.9
51-60	30.9
61-70	24.7
71-80	8.6
≥ 81	2.5
Complications/co-morbidities:	
Heart failure	11.8
Hypertension	9.1
Coronary heart disease	7.3
Ischemic stroke	6.8
Tuberculosis	5.5
Pneumonia	5.5
Others	< 5

Drug utilisation and clinical outcomes in the treatment of The T2DM patients are listed in Table 2. The most widely administered antidiabetic drug was a combination of rapid-acting and long-acting insulins received by 56 (69.1%) of the patients and insulin monotherapy by 18 (22.2%) of the patients. Table 2 also shows that, based on the results of random BGLs, most (60.5%) of the patients achieved good glycemic control or normoglycemia.

Table 2: Drug utilisation and clinical outcome in the treatment of T2DM patients (n = 81)

Drug therapy	% of patients provided antidiabetics
Monotherapy of insulin:	
Insulin aspart	2.5
Insulin aspart/protamine	22.2
Combination insulin:	
Insulin aspart + detemir	26
Insulin aspart + glargine	24.7
Insulin glulisine + glargine	11.1
Insulin glulisine + detemir	6.2
Insulin aspart/protamine + glargine	1.2
Insulin + oral antidiabetic drugs:	
Insulin aspart + metformin	1.2
Insulin aspart + metformin + glimepiride	1.2
Insulin aspart + insulin glargine + glimepiride	1.2
Insulin aspart + insulin detemir + metformin	1.2
Oral antidiabetic drug:	
Metformin	1.2
Oral antidiabetic combination:	
Metformin + glimepiride	1.2
Glimepirid + pioglitazone	1.2
Random BGL:	
Normoglycemia (< 200 mg/dl)	60.5
Hyperglycemia (≥ 200 mg/dl)	27.2
Hypoglycemia (< 70 mg/dl)	12.3

The incidence of DRPs in the treatment of T2DM patients is shown in Table 3. In this study, there were 68 DRPs identified, which affected BGLs. The most common DRPs found were drug interactions (45.6%) and inadequate dose (32.4%). Adverse drug reactions were found in 10 patients who experienced hypoglycemia as the effects of insulin or an oral

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antidiabetic sulfonylurea. Furthermore, the present study also found indication without drug therapy (2.9%) and ineffective provided drug (4.4%).

Table 3: Incidence of DRPs experienced by the T2DM patients

DRP category	Frequency	Percentage (%)	Description
Indication without drug therapy	2	2.9	Provision of rapid-acting insulin as monotherapy
Ineffective provided drug	3	4.4	Ineffective combination of rapid-acting insulin with metformin, ineffective combination of premixed insulin with long-acting insulin and metformin provided to patients with CHF grade III
Inadequate dose	22	32.4	The dose of insulin was not enough
Adverse drug reaction	10	14.7	Hypoglycemia
Drug interaction	31	45.6	The interaction of antidiabetic drugs with other drugs that have a hypoglycemic effect

The results of this study showed that 32 patients did not achieve the desired BGL in which there were 22 patients with hyperglycemia and the other 10 patients experienced hypoglycemia. DRPs have a significant correlation with changes in BGLs experienced by hospitalised patients with T2DM in HAM hospital. Relationship between DRPs with changes in BGL of the T2DM patients during treatment is shown in Table 4. As shown in the Table, the BGLs were classified into hyperglycemia, hypoglycemia, and normoglycemia. There was no significant relationship between indication without drug therapy with the hyperglycemic condition of the patients ($p = 0.064$). There was also no significant relationship between ineffective provided drug and hyperglycemia ($p = 0.079$). On the other hand, there was a significant relationship between inadequate dose and hyperglycemia ($p = 0.000$). Additionally, there was a significant relationship between adverse drug reaction and hypoglycemia ($p = 0.000$).

Table 4: Relationship between DRPs with changes in BGL of the T2DM patients (n = 81)

Primary Domain	Number of cases by clinical outcome			p-Value
	Hyperglycemia	Hypoglycemia	Normoglycemia	
Indication without drug therapy:				
Yes	2	0	0	0.064
No	20	10	49	
Ineffective provided Drug:				
Yes	3	0	0	0.079
No	19	10	49	
Inadequate dose:				
Yes	22	0	0	0.000
No	0	10	49	
Drug interaction				
Yes	46	31	94	0.000
No	4	0	10	
Adverse Drug Reaction				
Yes	0	10	0	0.000
No	22	0	49	

Discussion

The present study showed that T2DM was more prevalent in male compared to female. Other studies also found similar results [20], [21]. The age group of 51-60 years was more prevalent in this study. A study conducted in India revealed that the disease was more prevalent in the age group of 40-79 years [22]. This difference could be associated with the differences in social, economic conditions and lifestyle [23].

The most widely provided antidiabetic drug was a combination of rapid and long-acting insulins, followed by insulin as a monotherapy. This study supported the study undertaken in Malaysia, in which it was revealed that insulin was the most widely prescribed [20]. In contrast, another study revealed that metformin was the most commonly prescribed drug, followed by glibenclamide [21]. The difference was probably due to the different prescribing patterns between one hospital and others.

The American diabetes association recommends random blood glucose target of less than 200 mg/dL. A patient is categorised as hypoglycemia if he or she has BGL less than 70 mg/dL. Monitoring of BGL is commonly done by measuring the random BGLs on the last day of hospitalisation. To diagnose whether a patient is hypoglycemia, BGL was measured at the beginning of the incidence. In this study, 32 patients did not achieve the desired BGL consisted of 22 patients with hyperglycemia and 10 patients with hypoglycemia.

There were 68 DRPs experienced by those patients. The most frequently DRPs contributed to BGL was drug interaction, which had a significant relationship with hypoglycemia. Inadequate dose was the second most DRPs contributed to the change in BGL in which it had a significant relationship with hyperglycemia. Neither indication without drug therapy nor ineffective provided drug had a significant relationship with hyperglycemia. Drug selection problems tend to be in small amounts, so they did not affect changes in hyperglycemia. Indication without drug therapy was experienced by 2 (2.5%) of the hyperglycemia patients that received rapid-acting insulin as a monotherapy.

Additionally, inappropriate drug combinations consisted of an ineffective combination of rapid-acting insulin with metformin and combination of premixed insulin with long-acting insulin were received by 2 (2.5%) of the patients. Based on clinical practice guidelines, the first targeting treatment of hyperglycemia is to monitor basal BGL in fasting and pre-meal conditions. It can be achieved by administration of oral antidiabetic or insulin therapy. The combination of antidiabetic oral drug and insulin is started from the administration of basal insulin.

Rapid or short-acting insulin is used to achieve the target of prandial BGL. In a condition where BGLs throughout the day are still uncontrollable despite having received basal insulin, it is necessary to provide a combination of basal and prandial insulin [16], [18]. This present study also proved the presence of contra-indication in 1 patient (1.2%) with

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grade III heart failure in which the patient has administrated metformin as oral antidiabetic therapy. The previous study on DRP conducted by Zaman Huri and Fun Wee [20] found that approximately 24% of T2DM patients with hypertension and chronic kidney disease received metformin. Provision of metformin is a contraindication in this group of patients. This difference can be associated with many complicated factors, including the difference in prescribing pattern and the number of comorbidities suffered by the patients. In this study, there was a relatively small incidence of drug selection problems, but it is still required the attention of physicians when prescribing antidiabetic drugs to T2DM patients with complications [20].

Drug-related problems of inadequate dose related to the achievement of target BGLs were indicated in 22 patients with hyperglycemia. The result was different from the study conducted in Nigeria [21]. This difference cannot be explained due to the lack of information what drugs were found subtherapeutic dosages in the study. Besides, this study assessed the effect of DRPs on changes in BGLs as glycemic control. There were found an inadequate dose of insulin in this study related to the target of BGLs that were not reached, hyperglycemia. Clinical practice guidelines state that the initial dose of basal insulin can be started with 10 units, and its dose can be gradually increased by 2 units if fasting BGLs have not achieved the target [16]. Other literature declare that the initial daily dose of insulin can be started with 0.5-1.5 unit per kilogram body weight, then the insulin dose can be divided into basal insulin dose (50% of the initial daily dose) and prandial insulin dose (50% of the initial daily dose). Following the physiological condition of the body, insulin therapy is given once for basal and three times with prandial insulin for after-meal [24], [25], [26]. This problem also required the attention of health care providers to be able to increase the dose of insulin gradually when BGLs have not achieved the target of glycemic control.

The more the complications experienced by the patients, the more the number of drugs given to the patients and the higher the incidence of drug interactions [27]. This was in line with several studies which state that polypharmacy is closely related to DRP [28]. This was also proven based on the results of a study undertaken in Malaysia, which proved that there was a significant relationship between polypharmacy and drug interactions [20]. Increasing the number of prescripted drugs can increase the risk of drug interactions, poor control of BGLs and therapeutic outcomes. Therefore, routine monitoring and resolving of inappropriate clinical outcomes and clinically significant drug interactions are needed to optimise drug therapy [21]. The most common drugs involved in drug interactions were insulin with angiotensin receptor blocker, aspirin, quinolone and ace inhibitor. It was dissimilar to the study that reported aspirin, clopidogrel, simvastatin, amlodipine, beta-blockers, NSAIDs agents and ACE inhibitors were most implicated in drug interactions [20], [29]. The differences can be caused by the difference in complications experienced by these patients, so the prescribed drugs will be different. The drug interactions were identified in this study with major and moderate clinical significance levels, which can affect changes in BGLs based on ensured literature and evidence. Clinicians can still use the drug simultaneously with close monitoring of BGLs and followed by the appropriate actions [20].

In this study, hypoglycemia experienced by 10 T2DM patients is an undesirable drug therapy outcome due to drug interactions, and side effects resulted in the provision of insulin or oral antidiabetic drug. This was consistent with many studies reported incidences hypoglycemia related to the use of insulin and sulfonylurea [30], [31]. Hypoglycemia can occur at any time. Therefore, routine monitoring of BGLs and appropriate efforts are needed to avoid recurrence of hypoglycemia.

It can be concluded that DRPs has a significant effect on BGLs in the treatment of patients with T2DM. DRPs of dose selection affects the BGL of hyperglycemia and DRPs of drug interactions, and unwanted drug reactions affect the occurrence of hypoglycemia. With the proven influence of DRPs on changes in BGLs in the treatment of T2DM patients, the active role of pharmacists as a part of the healthcare providers is crucial to identify and resolve the presence of DRPs which in turns optimise the treatment of patients with T2DM.

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