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The effect of premixed insulin to blood glucose concentration in patients with type 2 diabetes mellitus

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Abstract:
Background: One of the therapies used to treat type 2 diabetes mellitus (T2DM) disease is combination insulin which consists of rapid-acting insulin and intermediate-acting insulin (premixed). This study aimed to examine the profile of premixed insulin related to blood glucose concentration and to identify the drug interactions due to the combination of premixed insulin with other drugs taken by T2DM patients.
Methods: This study was a prospective observational study with cross-sectional data that were analyzed descriptively. The respondents invited were T2DM patients with or without complication or comorbid disease who received premixed insulin with or without a combination of oral antidiabetic therapy in the Outpatient Unit of Universitas Airlangga Hospital, Surabaya. The research instruments used are data sheet, patient medical record, and fasting and postprandial blood glucose concentration.
Results: A total of 118 patients received premixed insulin therapy, but only 80 patients were included in the inclusion criteria. Based on types of insulin, the combination of 30% aspart and 70% protamine aspart was used by 91.25% T2DM patients, and a combination of 25% insulin lispro and 75% protamine lispro was used by 8.75% T2DM patients. There were 30.3% of patients who could achieve the target of 80–130 mg/dL in fasting blood glucose concentrations, and 35.1% of patients achieved the target of ≤180 mg/dL in postprandial blood glucose concentration. Drug interactions may occur in patients who use premixed insulin with glimepiride, lisinopril, fenofibrate, candesartan, irbesartan, and gemfibrozil.
Conclusions: In this study, premixed insulin have not reached the target of fasting and postprandial blood glucose concentrations in most patients.

Keywords: blood glucose, combination insulin, intermediate acting insulin, premixed insulin, rapid acting insulin, type 2 diabetes mellitus
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Introduction

Diabetes mellitus (DM) is a metabolic disease that arises in a person because of an increase in blood glucose concentrations above the normal level. This disease is caused by impaired glucose metabolism which occurs due to absolute or relative insulin deficiency. Diabetes is a complex chronic disease and requires ongoing medical care with multifactorial risk reduction strategy. Patients should be trained to apply self-management, receive support to prevent acute complications, and reduce the risks of long-term complications [1], [2].

Approximately 347 million people suffer from diabetes worldwide, so burdens increases globally, especially in developing countries [3]. The prevalence of diabetes for all age groups worldwide was estimated at 2.8% in 2000 and increased to 4.4% by 2030. The number of diabetics is projected to rise from 171 million in 2000 to 366 million in 2030. The number of DM patients in Indonesia tentatively will increase to 21.3 million in 2030 which is greater than at 8.4 million in 2000 [4].

Patients with type 1 diabetes must receive insulin therapy, while patients with type 2 diabetes mellitus (T2DM) can be given oral antidiabetic drugs or combination insulin. Based on the duration of work, the beginning of work, and the time to reach the peak concentration, insulin is divided into four types, such as long-acting (glargine, detemir, and degludec) and intermediate-acting [human neutral protamine Hagedorn (NPH)]

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as basal insulin, and rapid-acting (aspart, lispro, and glulisine) and short-acting (human regular) as prandial insulin [5].

Premixed insulin is a mixture of basal insulin and prandial insulin. Basal insulin usually uses intermediate-acting insulin, NPH, made by combining insulin and protamine to form a complex isofan. Protamine is a mixture of six major compounds and minor compounds with similar structures. These compounds are arginine-rich peptides. After subcutaneous injection, protamine is broken down by proteolytic tissue enzymes to increase insulin absorption [6], [7], [8].

Prandial insulin, usually used as a premixed mixture, is rapid-acting insulin. After subcutaneous injection, this insulin is more easily dissociated into a monomer form so that it is more rapidly absorbed, leading to rapid work-out and achieving peak work resembling endogenous insulin secretion. Insulin aspart, lispro, and glulisine are insulin belonging to fast-acting prandial insulin [6], [9].

There are many combinations of insulin preparations (premixed); one of them is a combination of rapid-acting insulin and intermediate-acting insulin with some comparisons. Therefore, it is necessary to conduct research to analyze the profile of the combination of rapid and intermediate-acting insulin in T2DM patients and to identify problems that can occur after its use. This study aims to examine the profile of a premixed insulin therapy related to laboratory data (blood glucose concentration) and to identify a drug-related problem (drug interactions) due to the utilization of premixed insulin with other drugs in T2DM outpatient at Universitas Airlangga Hospital Surabaya.

For many people with diabetes, glucose monitoring is a key for achieving the glycemic targets. According to American Diabetes Association (ADA) Guidelines 2018, the goal of therapy or glycemic target recommendation for DM patients is 80–130 mg/dL for fasting blood glucose and <180 mg/dL for postprandial blood glucose.

Subjects and methods

This study is a prospective observational study with a cross-sectional design. It was held in the outpatient unit of Universitas Airlangga Hospital Surabaya in 2017. Eighty patients as samples diagnosed with T2DM fulfilled the inclusion and exclusion criteria through 3 months of observation.

Inclusion criteria are patients diagnosed with T2DM with or without a complicated or comorbid disease and who receive a rapid and intermediate-acting combination insulin therapy with or without the combination of oral antidiabetic therapy (OAD). Exclusion criteria are discontinuing patients in this study. The research instruments used are data collecting sheets, patient medical records, and laboratory results (fasting and postprandial blood glucose concentration).

Data collected include gender, age, diagnosis, comorbidity and complication, dosage regimen of premixed insulin, and the utilization of other drugs. Fasting and postprandial blood glucose concentrations were noted after using premixed insulin for 3 months. Data were then analyzed descriptively based on categorical variables (percentage).

Results

There were 118 patients with T2DM who have received rapid and intermediate-acting combination (premixed) insulin for 1-month observation in the outpatient unit of Universitas Airlangga Hospital, Surabaya. Two types of premixed insulin are used at the hospital: 30% aspart with 70% inseminated aspart insulin combination and 25% lispro with 75% protamine lispro insulin combination. All patients were observed for 3 months, and 80 patients were included in the inclusion criteria. There were 39 female patients (48.8%) and 41 male patients (51.2%) as shown in Table 1.

Table 1: Demographic and clinical characteristics of T2DM patients.

Demographic and clinical characteristics (n = 80)	%
Gender	
– Male	51.2
– Female	48.8
Age	
– ≤45 years	
– Male	2.5
– Female	2.5

46–64 years	
– Male	35
– Female	31.3
– ≥65 years	
– Male	
– Female	15.3
Premixed insulin types	16.3
– 30% aspart with 70% inseminated aspart insulin	91.25
– 25% lispro with 75% protamine lispro insulin	8.75

Patients were also observed on the basis of age distribution. Table 1 illustrates the age distribution of T2DM patients in the outpatient unit of Universitas Airlangga Hospital, Surabaya. As many as 66.2% of the patients were between the ages of 46 and 64 years, dominated by male patients (35%) rather than females (31.3%), while 31.2% of the patients with the age distribution of ≥65 years predominantly consisted of female patients (16.3%) more than male patients (15.3%). There were only 2.5% patients aged ≤45 years with the same ratio of male patients and female patients.

Seen from Table 1, it also was found that 30% aspart with 70% inseminated aspart insulin was used more at 91.25% compared to 25% combination insulin lispro with protamine lispro 75% which amounted to 8.75%.

To determine the success of insulin therapy given to patients with T2DM, patients' blood glucose concentrations were measured. The blood glucose concentrations could be measured when patients were fasting and taking no glucose intake for 8 h with the target of 80–130 mg/dL. The blood glucose concentration can also be measured 2 h after eating. The glucose intake of 75 g after 2 h is targetted to be ≤180 mg/dL.

Table 2 showed that 30.3% of patients have achieved the targeted fasting blood glucose concentration at 80–130 mg/dL after using rapid-acting and intermediate-acting combination insulin for 3 months, while 69.7% of them have fasting blood glucose concentration above 130 mg/dL. The majority of patients (64.9%) have postprandial glucose concentration at >180 mg/dL (2 h after glucose intake of 75 g), while 35.1% of patients have successfully achieved the target of postprandial blood glucose concentration, which is ≤180 mg/dL after using rapid-acting and intermediate-acting combination insulin for 3 months.

Table 2: The achieved blood glucose concentration.

Type of examination blood glucose concentration	Achieved, %	Not achieved, %
Fasting	30.3	69.7
Post prandial	35.1	64.9

Table 3 explains the provision of premixed insulin therapy in patients with T2DM at Universitas Airlangga Hospital, Surabaya. There were 38.7% patients given premixed insulin therapy only without oral antidiabetic combination, while as many as 61.3% of patients got a combination with type 1 or 2 OAD.

Table 3: Use of premixed insulin with/without OAD combination.

Drugs	%
Premixed insulin	38.7
Premixed insulin + OAD	61.3
Combination with one type of OAD	
Premixed insulin + metformin	32.7
Premixed insulin + acarbose	18.4
Premixed insulin + glimepiride	8.2
Premixed insulin + gliquidon	6.1
Premixed insulin + glucodex	4.1
Combination with two types of OAD	
Premixed insulin + metformin + acarbose	8.2
Premixed insulin + metformin + glimepiride	10.2
Premixed insulin + metformin + gliquidon	4.1
Premixed insulin + metformin + glucodex	4.1
Premixed insulin + glimepiride + acarbose	2.0
Combination with three types of OAD	
Premixed insulin + metformin + glimepiride + acarbose	2.0

Some patients were not only diagnosed to have T2DM but also comorbidity or complication of T2DM while doing the medical examination in the Outpatient Unit of Universitas Airlangga Hospital as seen in Table 4.

Table 4: Comorbidity and complication.

	Number of cases	%
Complication		
Hypertensive heart disease without (congestive) heart failure	11	8.4
Atherosclerotic heart disease	10	7.6
Diabetic polyneuropathy	7	5.3
Hypertensive heart disease with (congestive) heart failure	6	4.6
Chronic ulcer of skin, not elsewhere classified	4	3.1
Chronic renal failure, unspecified	2	1.5
Congestive heart failure	2	1.5
Comorbidity		
Essential (primary) hypertension	35	26.7
Hyperlipidemia, unspecified	11	8.4
Gonarthrosis, unspecified	6	4.6
Hyperuricemia without sign inflame arthritis + tophaceous disease	6	4.6
Senile nuclear cataract	5	3.8
Cataract, unspecified	4	3.1
Dyspepsia	4	3.1
Low back pain	4	3.1
Cerebral infarction due to thrombosis of cerebral arteries	3	2.3
Cerebral infarction, unspecified	3	2.3
Acute upper respiratory infection, unspecified	2	1.5
Dermatitis, unspecified	2	1.5
Disorder of lipoprotein metabolism, unspecified	2	1.5
Other hyperlipidemia	2	1.5

Based on Table 4, a hypertensive heart disease without (congestive) heart failure was a common complication disease suffered by the patients (8.4%), and essential (primary) hypertension was a common comorbid disease (26.7%). Therefore, patients not only received premixed insulin therapy with/without oral antidiabetic for diagnosis of T2DM but also got an additional therapy, as shown in Table 5. The most common additional therapy that given was a supplement B-complex vitamin (23.75%), while most common antihypertensive therapy that given was Adalat Oros (18.75%).

Table 5: Use of other drugs.

Drugs	Number of patients	%
Adalat OROS (30 mg)	15	18.75
Amlodipin (10 mg)	11	13.75
Candesartan (150 mg)	6	7.5
Candesartan (16 mg)	2	2.5
Lisinopril (5 mg)	2	2.5
Concor (2.5 mg)	1	1.25
Simvastatin (20 mg)	8	10
Simvastatin (10 mg)	4	5
Gemfibrozil	2	2.5
Fenofibrat (300 mg)	1	1.25
Vitamin-B complex	19	23.75
Gabapentin (100 mg)	7	8.75
Allopurinol (100 mg)	2	2.5

The use of rapid intermediate-acting combination insulin with other drugs can cause drug-related problems, such as drug interactions, and potentially affect the effectiveness of the premixed insulin in patients with DM.

Discussion

Several aspects of T2DM that related to sex were identified as risk factors, such as pathophysiology, onset age, detection, or the management of T2DM. Moreover, the diabetes risk assessment tool based on the ADA guidelines includes sex-specific items. For example, male sex is acknowledged as a diabetes risk factor. Male patients are highly affected by DM and diagnosed at young age and levels of weight [10]. The prevalence of DM in male patients is higher than in females. Urban populations in developing countries are projected to double between 2000 and 2030 [4].

The study above found the same results as this study discovered. There were 118 patients with T2DM, and based on patients' demography, the number of male patients with premixed insulin therapy (51.2%) is higher than that of female patients (48.8%) as shown in Table 1. Based on age distribution, the age range of 46–64 years is the highest (66.2%) among other age ranges as Table 1 shows. This is also in accordance with the results of Basic Health Research (Riskesdas) Indonesia 2018 which found DM diagnosed by doctors (6.29%) has the highest prevalence at the age range 55–64 years [11]. In developing countries, the majority of diabetic people are between 45 and 64 years old. By 2030, it is estimated that the number of people with diabetes aged >64 years will be more than 82 million in developing countries and 48 million in developed countries. Indonesia is one of 10 countries estimated to have the highest number of people with diabetes in 2000 and 2030 with 21.3 million people with diabetes [4]. Older adults are at high risk for suffering from T2DM due to the combined effects of increasing insulin resistance and impaired pancreatic islets along with aging. Age-related insulin resistance appears to be primarily associated with adiposity, sarcopenia, and physical inactivity, which may partially explain the disproportionate success of the intensive lifestyle intervention in older patients. The ADA recommends that overweight adults with risk factors and all adults aged >45 years should be screened in the clinical setting every 1–3 years using either fasting plasma glucose test, A1C, or oral glucose tolerance test [10].

Insulin treatment is a necessity of life for many patients with T2DM. It is still a cornerstone for T2DM treatment to maintain optimal blood glucose level. Since the disease is not well controlled in many patients, treatment given to patients who use basal insulin and require additional mealtime insulin can be intensified by adding a short-acting human insulin (mealtime insulin) or by switching it to a premixed insulin regimen. The formulations combine a fixed combination of short-acting insulin or rapid-acting insulin with an intermediate-acting protamine component, which provides mealtime and basal blood glucose control in one injection. Compared to self-mixed insulins, premixed insulin formulations contain basal and mealtime insulin components, offer convenience, and play an important role in the T2DM treatment. The result of the previous study indicates that the use of a premixed insulin analog performs a similar improvement in the glycemic control and hypoglycemic outcomes compared to that in the basal-plus regimen. These results indicate that premixed analog insulin may be an effective alternative to manage hyperglycemia in patients with T2DM [12].

Biphasic insulin aspart 70/30 and insulin lispro 75/25 are the most commonly used biphasic or premixed insulin analog. These dual-release formulations combine a soluble and rapid-acting component with a protaminated insulin analogue portion that has a prolonged duration of action. Compared to human premixed insulin (HPI), premixed insulin analog has a faster onset of action (5–15 min) and earlier peak (1–2 h) for the first component and a relatively steady second component lasting up to 16 h. These characteristics lead to an improved pharmacodynamic effect, with favorable biochemical and physiological blood-glucose-lowering actions. The premixed insulin analog is associated with substantially less hypoglycemia than HPI, especially nocturnally, which would conceivably translate into less treatment-related worry and higher acceptability for patients [13].

Two compositions of premixed insulin in this study include aspart protamine combination and lispro protamine combination. As much as 30% aspart and 70% protaminated aspart was used more by clinicians (91.25%) compared to 25% insulin lispro and 75% protamine lispro (Table 1). The differences of these two types of insulin combinations are the type of rapid-acting insulin (aspart and lispro) and the composition ratio. As much as 30% aspart and 70% protaminated aspart have onset of action of 10–20 min, peak time of 60–240 min, and 45% total activity occurring in the first 4 h, while 25% lispro and 75% protamine lispro have onset of action of 15–30 min, peak time of 2.6 h, and 35% total activity occurring in the first 4 h. However, they have the same duration of action of 18–24 h [14]. The previous study investigated the efficacy and safety of aspart and lispro delivery by insulin pump combined with metformin in patients with newly diagnosed T2DM, and the result showed that both aspart and lispro had similar function in controlling the level of blood glucose and blood glucose fluctuation. The study also analyzed the hypoglycemia episode in the two groups, and the data indicated that aspart and lispro had no difference in hypoglycemic events in new diagnosis of T2DM. Because of the

considerable effect of aspart and lispro, they can both be regarded as suitable insulin intensive treatment options [15] . This premixed insulin can fulfill the needs of basal insulin and prandial insulin in one dosage form. It is very important to implement an insulin therapy to patients who are likely to adhere because non-adherence to pharmacotherapy has been associated with unfavorable outcomes [16].

Premixed insulin also has a limitation in the ratio of composition. Both components of insulin do not always match the individual dose needed by patients. This can be influenced by blood glucose concentrations and patient conditions associated with complications, comorbidity, and various responses of glucose reduction to insulin administration in each patient. A twice-daily injection, before breakfast and dinner, is the most common method that uses premixed insulin and provides both basal and prandial coverage [13]. The addition and reduction of the dose were evaluated monthly through the examination of the patient's blood glucose concentration.

A previous study about lowering fasting glucose showed that premixed insulin analogues were less effective than long-acting insulin analogues (administered alone) in lowering fasting glucose. In contrast to fasting glucose, premixed insulin analogues were more effective than long-acting insulin analogues in lowering postprandial glucose and A1c [14]. After 3-month observation on premixed insulin used, the blood glucose concentration was examined. Table 2 shows that 30.3% of patients have achieved fasting blood glucose concentration of 80–130 mg/dL, and 2-h postprandial blood glucose concentration of ≤180 mg/dL is achieved by 35.1% of patients. This suggests there were still many patients who have not been able to achieve the targets of blood glucose concentrations. It can be associated with complications and comorbidity that affect the insulin response to the level of blood glucose. The number of drug-related problems, especially interaction of premixed insulin with other drugs consumed by patients, may affect the insulin performance. It could also be due to improper use of insulin in a patient as non-adherent use of insulin because patients use self-insulin without supervision from health personnel. Therefore, it is necessary to conduct further research about an assessment of how a patient with T2DM uses insulin, education to use insulin properly, and the effect of insulin on the target of patient's blood glucose concentration.

To achieve the target of blood glucose concentration, patients got premixed insulin. In Table 3, the data showed 61.3% of patients also received oral anti-diabetes to reduce blood glucose concentrations in addition to using premixed insulin. The ADA and the European Association for the Study of Diabetes consensus recommends the continuing use and adjustment of the existing anti-diabetic agents upon the beginning of insulin therapy. Customization to specific clinical situations and patient characteristics should be done. If possible, metformin drug intake should be continued by insulin-treated patients. Combining insulin with a sulfonylurea may be of least clinical advantage since it has the propensity to increase hypoglycemia. The presence of comorbid conditions such as nephropathy and congestive heart failure may contraindicate the use of metformin and thiazolidinedione with insulin [13].

Metformin is the first step of therapy for patients with DM. Adding metformin to an insulin therapy can lower the requirements of insulin and improve metabolic control. Metformin also decreases the risk of cardiac vascular disease, as well as the absence of risk of hypoglycemic side effects [1], [9]. A premixed insulin analogue combined with oral antidiabetic agents was probably more effective than a single premixed analog in lowering the postprandial glucose levels (pooled mean difference = −5.8 mg/dL, 95% CI: −15.7 to 4.1 mg/dL; p = 0.25) and the fasting glucose levels [14].

Some complications and comorbidity also are described in Table 4. Hypertensive heart disease without (congestive) heart failure was the most frequent complication disease (8.4%) followed by atherosclerotic heart disease (7.6%). Atherosclerotic cardiovascular disease is defined as acute coronary syndromes, a history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, transient ischemic attack, stroke, or peripheral arterial disease as the leading cause of morbidity and mortality for patients with diabetes [1]. Multiple cellulars and molecular pathophysiologic factors contribute to atherosclerotic cardiovascular disease. Patients with T2DM have greater atherosclerotic plaque burden, higher atheroma volume, and smaller coronary artery lumen diameter than patients without DM. Atherosclerotic cardiovascular disease is caused by numerous processes, such as hyperglycemia, insulin resistance or hyperinsulinemia, dyslipidemia, inflammation, reactive oxygen species, endothelial dysfunction, hypercoagulability, and vascular calcification [17].

Hypertension and T2DM are the common comorbidities. Hypertension is an important risk factor for diabetes-associated vascular complications because it is characterized by vascular dysfunction and injury [18]. In this study, primary hypertension was the most accompanying disease (26.7%) as shown in Table 4. Hypertension is a common diabetes comorbid the prevalence of which depends on the type of diabetes, age, body mass index, and ethnicity and becomes a major risk factor for both atherosclerotic cardiovascular disease and microvascular complications. T2DM usually coexists with other cardiometabolic risk factors [1]. Therefore, patients get therapy to overcome not only diabetes itself but also comorbid and other diseases. The other most used drugs are shown in Table 5. The most used oral antihypertensive drug is Adalat oros® (18.75% patients)

containing nifedipine oros. The use of other drugs especially oral anti-diabetes becomes a consideration due to the potential interactions with premixed insulin that can increase the side effects of hypoglycemia. Drug interactions are shown in Table 6. There are potential interactions in the use of glimepiride, lisinopril, irbesartan, candesartan, gemfibrozil, and fenofibrate with premixed insulin, so regular monitoring of blood sugar levels is needed [19], [20].

Table 6: Drug interaction between premixed insulin and other drugs [9], [19].

Drugs interaction	Severity	Mechanism	Effect	Management
Premixed insulin with sulfonylurea (glimepiride)	Moderate	Increase the insulin	Increase the side effect of hypoglycemia	Blood glucose concentration monitoring
Premixed insulin with Angiotensin Converting Enzyme (ACE) inhibitor (lisinopril)	Moderate	Increase the use of glucose and insulin sensitivity	Increase the side effect of hypoglycemia	Blood glucose concentration monitoring
Premixed insulin with fibrate (gemfibrozil)	Moderate	Lower insulin resistance	Increase the side effect of hypoglycemia	Blood glucose concentration monitoring
Premixed insulin with fibrate (fenofibrate)	Moderate	Lower insulin resistance	Increase the side effect of hypoglycemia	Blood glucose concentration monitoring
Premixed insulin with Angiotensin Receptor Blocker (ARB) (irbesartan and candesartan)	Moderate	Increase the use of glucose and insulin sensitivity	Increase the side effect of hypoglycemia	Blood glucose concentration monitoring

Further study is needed to identify the cause of unachieved patient's blood glucose level which may be due to patients' disobedience to the improper use of insulin which may decrease the effectiveness of insulin because patients use their own insulin without any supervision from health personnel. Further studies can be done by assessing and educating patients who receive a rapid-acting and intermediate-acting combination insulin therapy. The comparison study is also required to identify the effectiveness and safety among types of insulin in patients with T2DM.

Conclusions

The aspart premixed insulin is more widely used than lispro premixed insulin in Universitas Airlangga Hospital. Most patients have not reached the target of fasting and postprandial blood glucose concentrations. This can be influenced by patient conditions associated with complication, comorbidity, and various responses of glucose reduction to insulin administration in each patient. Drug-related problems especially potential interactions of premixed insulin with glimepiride, lisinopril, fenofibrate, candesartan, irbesartan, and gemfibrozil occurred in patients, so regular monitoring of blood glucose concentration is needed.

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