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Original research

Patient-factors associated with metformin steady-state levels in type 2 diabetes mellitus with therapeutic dosage

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ABSTRACT

Aims: This prospective study aimed to analyze metformin steady-state concentration in repeated constant dosage and the influencing patient-factors as well as to correlate them with glycemic control.
Methods: The validated HPLC-UV method was used to examine metformin steady-state concentration, while FBG and glycated albumin were used as the parameters of glycemic control during metformin administration.
Results: A total of 82 type-2 diabetes patients were involved with 32.1% of them having metformin Css^{min} and 84.1% having Css^{max} of metformin within the recommended therapeutic range. One patient had metformin Css that exceeded minimum toxic concentration despite his normal renal function and administered therapeutic dosage of metformin. Higher Css^{max} was found in patients with metformin monotherapy, while patients with longer duration of metformin use had significantly higher Css^{min}.
Conclusions: Along with initial hyperglycemia and eGFR, metformin Css^{min} became the only parameter that influenced FBG level ($P < 0.05$). Duration of previous metformin use should be considered in the strategy of optimizing metformin dosage. The type-2 diabetes patients with obesity are more suggested to take shorter interval of metformin administration (or possibly with sustained-release formulation) to keep Css^{min} within the therapeutic range.

Introduction

Diabetes mellitus is a chronic metabolic condition affecting 10 million of Indonesian population mostly with type 2 diabetes mellitus (T2DM) in 2015 [1]. While metformin should be prescribed routinely for patients whose blood glucose cannot be controlled merely by lifestyle modification, the plasma steady-state concentration (PSSC) of metformin often seems to be neglected in clinical setting because it is not a priority in therapeutic drug monitoring.

Metformin PSSC could estimate optimum doses, particularly in elderly patients, patients with renal impairment, or even in specific conditions such as pregnancy with PCOS or obesity, due to changes in its pharmacokinetic profiles. In addition, PSSC could confirm inadequacy of metformin doses as well as metformin incompliance [2]. PSSC is achieved after repetitive administrations of metformin at a constant frequency which is expected within the therapeutic range [3]. However, the proposed upper limit of metformin concentration, which is 5 μg/ml to avoid lactic acidosis, should be considered in the metformin therapy management.

To date, studies of metformin PSSC have merely focused on minimum steady-state concentration (Css^{min}) in relation to genetic factors [4–6] despite the widely-acknowledged fact that Css^{max} is more recommended for measuring the safety of long-term drug use [3]. Although lactic acidosis in some patients with a higher plasma metformin concentration remains debatable, several studies have found such condition [7–9], making measuring this level become important to optimize the dosage and prevent metformin-associated lactic acidosis (MALA) [3]. However, most of those studies were conducted retrospectively with unidentified variety of doses, duration, and last metformin dose administered. Therefore, this present prospective study attempts to determine the trough and peak PSSC of metformin with constant dosage and identical time interval (τ) as well as to identify patient-factors associated with metformin PSSC and glycemic control to provide a new approach to clinical recommendation for metformin administration in T2DM.

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Table 1
Peak concentrations of metformin at steady-state for multiple doses of 500 mg metformin per 12 h.

Patient Grouping	Frequency (%)	Css^{min} (μg/mL) (P Value)	Css^{max} (μg/mL) (P Value)
Sex			
Male	16 (19.5)	0.706 ± 0.546	1.698 ± 1.017
Female	66 (80.5)	0.575 ± 0.429 (0.396)	1.845 ± 0.921 (0.577)
Age (years)			
< 50	33 (40.2)	0.616 ± 0.430	1.815 ± 1.117
≥50	49 (59.8)	0.589 ± 0.470 (0.792)	1.817 ± 0.804 (0.992)
BMI (kg/m^2)			
< 30	69 (84.1)	0.623 ± 0.472	1.822 ± 0.944
≥30	13 (15.9)	0.475 ± 0.321 (0.282)	1.787 ± 0.931 (0.903)
eGFR ($mL/min/1.73\,m^2$)[c]			
40–60	6 (7.3)	0.957 ± 0.546	2.244 ± 0.529
> 60–120	72 (87.8)	0.586 ± 0.439	1.832 ± 0.954
> 120	4 (4.9)	0.298 ± 0.275 (0.059)	0.896 ± 0.416 (0.075)
Cl_{cr} (mL/min)[d]			
40–60	9 (11.0)	0.638 ± 0.563	1.907 ± 0.812
> 60–120	65 (79.3)	0.607 ± 0.373	1.899 ± 0.931
> 120	8 (9.8)	0.500 ± 0.844 (0.796)	1.136 ± 0.900 (0.068)
Duration of T2DM (years)			
< 5	29 (35.4)	0.593 ± 0.475	1.824 ± 1.118
≥5	53 (64.6)	0.603 ± 0.444 (0.923)	1.812 ± 0.832 (0.955)
Duration of routine use of 500 mg metformin twice daily (weeks)			
2–6	18 (22.0)	0.415 ± 0.365	1.584 ± 0.946
> 6	64 (78.0)	0.652 ± 0.463 (0.049)[a]	1.882 ± 0.930 (0.235)
Antidiabetics Regimen[b]			
Metformin Monotherapy	35 (43.2)	0.611 ± 0.415	2.168 ± 0.927
Combination with Sulfonylureas	46 (56.8)	0.587 ± 0.488 (0.819)	1.543 ± 0.868 (0.003)[a]

[a] Significance level < 0.05.
[b] One patient with insulin combination therapy was excluded.
[c] CKD-EPI formula.
[d] Cockcroft-Gault formula using IBW for the obese patients.

Subjects, materials and methods

Study design

T2DM patients aged 30–60 years originating prospectively in six primary healthcare centers of Yogyakarta Province, Indonesia were involved. The study included patients administrated with metformin 500 mg twice daily for at least 2 weeks in either single or combined with other antihyperglycemic agents. There were restrictions on the metformin daily dose, time interval, and other medications. Patients taking cimetidine, nifedipine, or furosemide were excluded due to potential interaction that might cause changes in metformin pharmacokinetic [10]. Exception also applied to patients under systemic steroid treatment [11]. Patients with serum creatinine level ≥1.5 mg/dL in men and ≥1.4 mg/dL in women [12], history of thyroid dysfunction [13], and chronic liver disease [14], as well as patients not adhering to metformin therapy could not participate in this research. The study was approved by the Ethics Committee of the Faculty of Medicine of Gadjah Mada University (No. KE/FK/648/EC) and conducted in accordance with the Declaration of Helsinki. A written informed consent was obtained from all the subjects.

Steady-state pharmacokinetics of metformin assay

To measure trough PSSC, blood samples were taken immediately before administration of the next dose (pre-dose). Subsequently, blood samples taken 3.5 ± 0.5 h after metformin ingestion were used to measure peak PSSC (post-dose). Determination of metformin plasma concentrations was done using validated RP-HPLC assay with Sunfire® C-18 column 4.6 × 150 mm × 5 μm from Waters and SM7 injector with UV detector at 233 nm. All parameters for the bioanalytical method have fulfilled the Guidance for Bioanalytical Method Validation by FDA. The linearity of standard curve (r) was 0.9999 with < 15% accuracy value (% diff) and < 15% precision value (CV). The obtained selectivity value (CV) was < 15% while the CV of recovery ranged from 1.22% to 1.89% (in review). Metformin PSSC was used to estimate the elimination rate followed by calculation of metformin half-life.

$$K\ (/hour) = \frac{ln\left(\frac{Css^{max}}{Css^{min}}\right)}{8}$$

$$t_{1/2}\ (hour) = \frac{0.693}{K}$$

[3]

Statistical analysis

The obtained PSSCs were each presented as the mean ± SD. Independent *t*-test and one-way ANOVA were performed to compare PSSCs for each group of patient characteristics. Spearman-test was used to investigate patient factors in metformin PSSC and to analyze the influence of metformin PSSC on FBG and GA. Linear regression was

used to analyze patient-factors affecting the glycemic control. A p value ≤0.05 was considered statistically significant.

Results

PSSC examination was performed for 83 out of 86 patients, while three of them did not follow the procedure. Meanwhile, one patient had a history of routine use of 1500 mg/day metformin before participating in this study, given therefore a separate discussion.

Steady-state pharmacokinetics of metformin

There were 82 T2DM patients with prescribed 500 mg metformin twice daily. One patient participated in blood sampling only for Css^{max} because of his time constraint. Therefore, 81 plasma concentrations for Css^{min} and 82 for Css^{max} were collected. (Table 1).

Table 1 shows that metformin use > 6 weeks had 1.57 higher Css^{min} than that in patients with 2–6 week administration ($P < 0.05$). In the monotherapy group, Css^{max} was also more significant, reaching 1.44-fold, compared to that in metformin-sulfonylurea patients (glibenclamide or glimepiride). It was also found that metformin $t_{1/2}$ in patients using it for 2–6 weeks and > 6 weeks was each 4.01 h and 6.27 h (not displayed). There was a positive correlation between age and Css^{max} as well as Css^{min} while increased BMI caused a decrease in metformin Css^{min}.

Steady-state pharmacokinetics of metformin in patient with history of 1500 mg/day use

A 58.67-year-old male patient with BMI 20.81 kg/m^2 has been diagnosed as having T2DM for ± 6 years with a history of taking metformin 1500 mg/day. The patient had a stroke in February 2015, with no history of liver disorder, COPD and asthma, alcohol consumption, intravenous contract medium use, or sepsis. His eGFR was normal, 94 mL/min/1.73 m^2, and he was given valsartan and aspirin. After routine taken of metformin 1500 mg/day since 2014, his dose has been reduced to 500 mg twice daily since January 2015. His PSSC measurement procedure was identical to that of the other 82 patients. His metformin chromatogram is presented in Fig. 1.

The AUC in chromatogram shows that the metformin Css^{min} and Css^{max} reached 15.175 µg/mL and 16.198 µg/mL, respectively (or 117.487 µmol/l and 125.407 µmol/l). The patient was then given a blood gas analysis (Table 2).

Correlation between metformin PSSC and glycemic control

Among 35 patients, 32 were examined for FBG, two patients were not fasting, while one patient did not take metformin on day 39. Since glycated albumin (GA) has been well known for its accuracy on non-fasting subjects, the two patients remained eligible for GA test [15]. In total, 34 patients were given GA examination. The patient-related factors influencing FBG and GA are described in Table 3.

Table 2
Biochemical parameters of a patient with T2DM whose metformin Css exceeded MTC.

Parameter	Reference	Result
Creatinine	0.7–1.2 mg/dL	0.89
eGFR	> 60 mL/min/1.73 m^2	94
Clcr	> 60 mL/min	109.24
Initial FBG	< 100 mg/dl	148
Initial GA	11–16%	25.81
Final FBG	< 100 mg/dl	136
Final GA	11–16%	27.46
Arterial pH	7.35–7.45	7.479
pCO_2	35.0–45.0 mmHg	28.9
pO_2	80–100 mmHg	153.80
O_2 Saturation	75.0–99.0%	98.50
Bicarbonate (HCO_3^-)	22–26 mmol/L	21.7
Total CO_2	23.0–27.0 mmol/L	22.5

Table 3
Patient factors affecting glycemic control after routine administration of 500 mg metformin twice daily for 6 weeks.

Dependent Variable	Independent Variable	Coefficient	Correlation Coefficient	P Value
Final FBG	Duration of previous metformin therapy	−33.335	−0.415	0.010*
	Initial GA	3.428	0.513	0.002*
	Css^{min}	−27.215	−0.296	0.160
	Css^{max}	13.275	0.321	0.126
FBG Changes	eGFR	1.202	0.425	0.005*
	Initial FBG	−1.327	−1.277	0.000*
	Initial GA	4.491	0.497	0.012*
	Css^{min}	−40.719	−0.328	0.042*
	Css^{max}	24.444	0.438	0.015*
Final GA	eGFR	0.075	0.266	0.037*
	Initial FBG	−0.059	−0.575	0.003*
	Initial GA	1.036	1.156	0.000*
	Css^{max}	1.608	0.290	0.014*
GA Changes	eGFR	0.074	0.381	0.035*
	Initial FBG	−0.056	−0.780	0.000*
	Css^{max}	1.591	0.414	0.012*

* Significance value < 0.05; C^{ss} steady-state concentration; FBG fasting blood glucose; GA glycated albumin; eGFR estimated glomerulus filtration rate.

Both Css^{max} and Css^{min} insignificantly affected final FBG with medium correlation. The finding not in line with the prediction was shown by the positive correlation between metformin Css^{max} and glycemic response. Different from Css^{max}, an expected correlation appeared between Css^{min} and final FBG as well as FBG changes. However, this study found that there was no influence of Css^{min} on GA. The patient factors that significantly influenced final GA were eGFR, initial GA, and initial FBG as well as metformin Css^{max} ($P < 0.05$). In addition, a stronger negative correlation appeared between initial FBG and

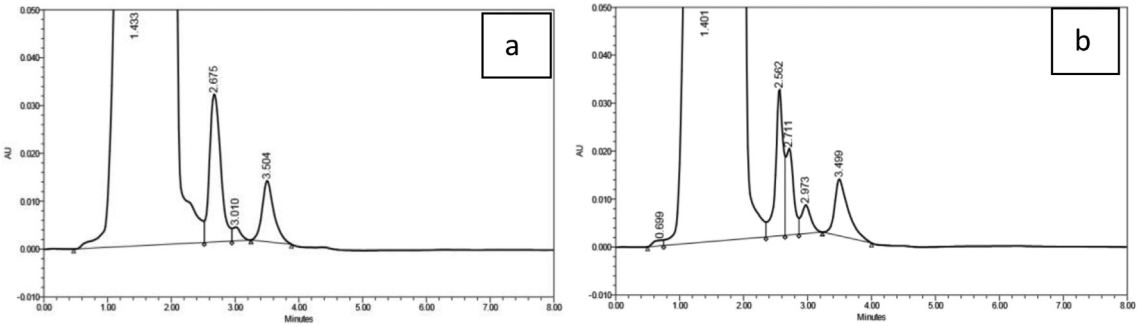

Fig. 1. Chromatogram of plasma metformin in a patient with history of taking 1500 mg metformin per day: (a) Css^{min}, (b) Css^{max}.

GA changes (r −0.780; P 0.000) compared to when final GA became a dependent variable.

Discussion

Pharmacokinetics of metformin steady-state

This present study was the first to demonstrate the trough as well as peak PSSCs of metformin with a fixed interval between doses of 500 mg metformin in 82 T2DM patients. The obtained Css^{min} in this study was relatively lower than the peak concentration in single dose of 500 mg metformin administered to 6 healthy subjects, which was 1.02 ± 0.34 μg/mL [16], as well as to 24 healthy subjects with Cp^{max} 1.75 ± 0.11 μg/mL (19). Since it has been acknowledged that the half-life of metformin elimination is ± 5 h in T2DM patients with a normal renal function [17], the administration of metformin per-12 h (2.4-fold $t_{1/2}$) led to lower Css^{min} compared to the peak concentration in single dose of 500 mg metformin. In this study, administration of 500 mg metformin twice daily did not form accumulation, proven by the obtained R (drug accumulation) of 1.04. This finding strengthened the previous result, in which the obtained metformin $t_{1/2}$ was relatively similar to $t_{1/2}$ in literature (6.2 h) based on the pharmacokinetic profile of 500 mg metformin in single dose [18,19].

This research also found an enormous variety of metformin Css^{min} (> 100-fold) and Css^{max} (15-fold). The patients were given an identical formulation of metformin, which was the generic dosage form produced by national pharmaceutical industry; therefore, the effect of formulation could be neglected.

This present study became the first to indicate that the duration of prior metformin use could significantly influence Css^{min} in a chronic therapy involving T2DM patients; this has never been found in previous studies. Deep compartment is known to be responsible for metformin Css^{min} variation due to a difference in the duration of multiple dose that cannot be identified in single dose administration [16]. Higher Vd.F represents the degree of equilibrium and Vd that could only be identified in a study involving metformin multiple doses. The findings of this study could be caused by inter-compartmental equilibrium in metformin Vd to erythrocytes [20]. The study of 9 T2DM patients found lower concentration of metformin on day 1 compared to that on either day 5 or day 6 [20]. Therefore, this study confirmed the deceleration of average metformin elimination, reaching 1.57-fold, due to distribution in the deep compartment into erythrocytes among patients with a history of metformin use > 6 weeks, which caused a significant difference in metformin $t_{1/2}$ ($P < 0.05$). Therefore, the use of blood as a biological sample is not recommended for metformin TDM [21,22] based on the rapid elimination of metformin and a potential delay in examining plasma metformin concentration (since metformin is a non-priority drug in TDM), which makes its level lower than the actual result [23]. However, MTC in erythrocytes is yet unknown, making plasma the most selected bio-fluid samples. Therefore, this study emphasized that not only should the dose, administration and sampling time be controlled, but the previous duration use should also be considered when conducting a study of metformin trough concentration although the time to reach steady-state has been estimated based on metformin $t_{1/2}$. This study recommends further investigations into metformin Css^{min} currently used as an independent variable for the effect of genetic variations especially on metformin-transporter coding genes [24,4].

Metformin concentration has been widely acknowledged to have a correlation with lactate metabolism. If plasma metformin concentration exceeds MTC, metabolic disorder will have a serious effect. To date, the possible interaction between metformin and sulfonylureas at pharmacokinetic level has yet to be identified. This study found that patients with monotherapy were at relatively greater risk of lactic acidosis due to the higher obtained Css^{max} compared to the combination therapy group ($P < 0.05$). This significant difference was possibly caused by two conditions. The first was potential interaction between metformin and food. A study found an extended t_{max} median up to 1.5 h when metformin was co-administered with food [25]. Furthermore, the time delay to achieve Cp^{max} was shorter, only 37 min, shown by subjects who took metformin along with food [26]. Another study also found relatively similar extended t_{max} (30 min) in a group consuming high-fat diet. In addition, 1.18-fold Cp^{max} was found in a fasting group though with insignificantly different metformin AUC [27]. However, a RCT study showed that high standardized-fat breakfast did not influence the bioequivalence parameters between fasting group and breakfast group [25]. Another study investigated metformin interaction with four diet types on pharmacokinetic parameters of metformin. Compared to the fasting condition, AUC and Cp^{max} showed a bioequivalent result except with high-carbohydrate diet that showed a slight decrease in those parameters [28]. Meanwhile, the procedure of this present study determined that patients with combination therapy took sulfonylurea together or maximum 15 min prior to breakfast at 6 a.m., while the metformin-monotherapy group was also suggested to have breakfast at 6 a.m. Prior to Css^{max} examination, 500 mg metformin was administered along with non-standardized snacks for all subjects. Consequently, possible metformin-food interaction that might cause differences in Css^{max} could not be neglected.

The second likely reason was the obtained average Css^{min} that was higher in the metformin-monotherapy group (1.09-fold) compared to that of the other group though statistically they were insignificantly different ($P > 0.05$). This was also indicated by the significantly strong correlation ($r = 0.648$) between Css^{min} and Css^{max}.

Gender insignificantly correlated with metformin PSSC. However, the study found higher metformin Css^{min} in male subjects and lower Css^{max} compared to female subjects ($P > 0.05$). Analysis of 47 data sets from 26 studies of bioequivalence reported to FDA revealed that ± 75% of the data found higher Css^{max} in female subjects [29]. In general, intestinal transit time of solid dosage form is longer in women than in men, which may lead to higher metformin Css^{max} [30]. Therefore, women are more susceptible to higher bioavailability [31], including that of metformin. Meanwhile, metformin Css^{min} was found to be lower in female possibly due to their higher BMI (26.16 kg/m^2 compared to 22.38 kg/m^2). Since metformin is hydrophilic, BMI does not affect its Vd [32]. The difference was possibly caused by increased excretion of metformin due to higher eGFR and more effective tubular secretion, resulting in lower Css^{min} in women than in men.

A positive correlation was found between age and metformin PSSC. This is in line with a study of 36 respondents which found that age was a predictive factor for metformin pharmacokinetic profile [33]. Older age leads to a decrease in the Vd of hydrophilic drugs, such as metformin. Along with reduced renal function in older age, metformin could experience reduced renal excretion and increased concentration in plasma [34]. Since this present study excluded geriatric patients (> 60 years old), the correlation was very weak ($r < 0.2$).

In addition, increased IMT means reduced metformin PSSC. Different PSSCs were shown more clearly in Css^{min} than in Css^{max} (1.31-fold compared to 1.02-fold). As predicted, Css^{min} could better reflect metformin disposition, particularly the renal elimination affected by BMI, as opposed to Css^{max}. In obese patients, metformin elimination is higher than in subjects with normal BMI or likely lean body due to increased eGFR and tubular secretion, while increasing mass of fat in obese patients does not affect its Vd [35,36].

Based on these findings, two recommendations in clinical setting are provided. First, not only age and renal function, duration of previous metformin use should also be considered in the strategy of optimizing metformin dose, or when the glycemic response of metformin 1000 mg/day has yet to be achieved, it is better to combine metformin with other antihyperglycemic agents (if necessary) to prevent lactic acidosis due to metformin accumulation in chronic therapy. Although the recommended maximum dose of metformin is not affected by sex, BMI, and T2DM duration, obese T2DM patients are more suggested to take shorter interval of metformin administration (or possibly with

sustained-release formulation) to keep Css^{min} within the therapeutic range.

This study also found one patient with a history of taking 1500 mg/day metformin and Css exceeding MTC. High concentration of metformin is a risk factor for lactic acidosis as shown by a study involving 7 patients suffering from lactic acidosis with plasma metformin concentration reaching 256–682 μmol/l [37]. Although his PSSCs were higher than MTC, he did not have lactic acidosis. The absence of nausea, vomiting, and abnormal pH (< 7.37) [38] in the patient was similar to another finding that showed no correlation between plasma metformin concentration and prognosis of MALA [39–41] as well as between metformin concentration and lactic acidosis. This was also indicated by 52 patients with Clcr < 60 mL/min; no correlation was found between Css^{av} and lactate concentration in both metformin-monotherapy and metformin-sulfonylurea groups [18]. In general, the risk of MALA can increase in hypoxia, such as in myocardial infarction, acute heart failure, or septicemia as well as liver and renal disorders [38,42]. Therefore, metformin accumulation does not have such a serious effect as lactic acidosis if it is not accompanied by particular pathological conditions [43].

The patient was found to have taken ECG test, and the result was normal heart function. Since he did not have such risk factors, the high metformin PSSC would possibly have no clinical effects. However, the database of pharmacovigilance studies from 1985 to October 2013 found a significantly positive correlation among plasma metformin concentration, lactate concentration, and creatinine level (r > 0.5). In addition, there was a significantly strong negative correlation between metformin concentration and blood pH (r 0.65) [8]. Therefore, although the patient experienced no clinical effects, extended elimination that could possibly occur in plasma metformin accumulation (> 5 μg/mL) needs monitoring. Furthermore, in such case, metformin use combined with other antihyperglycemic drugs is recommended (as opposed to increasing metformin dose) when the glycemic target is not yet reached to prevent possible lactic acidosis.

Correlation between metformin steady-state concentration and glycemic control

When the obtained metformin Css was compared to the recommended therapeutic range, only 32.1% patients had Css^{min} within the therapeutic range, while those having Css^{max} within the therapeutic range reached 84.1%. Although this study excluded patients aged > 60 years and involved only 6 patients (17.65%) having BMI ≥ 30 kg/m^2, the findings had been in line with another study involving 1856 T2DM patients which showed that both age and BMI were not the covariates influencing the efficacy of antihyperglycemic therapy [44]. Therefore, obese and non-obese T2DM patients would derive an equal benefit of metformin monotherapy. This is in accordance with a phase IV clinical trial in 371 T2DM patients which found that glycemic response after metformin-monotherapy were insignificantly different among patients with various BMI [45]. Along with initial hyperglycemia and Css, eGFR was correlated with FBG changes, final GA, and GA changes with a strong positive correlation. This means that the higher the eGFR, the better the metformin renal excretion, causing reduced bioavailability of metformin and thus decreased glycemic response.

As predicted, previously longer duration of metformin administration would result in lower final FBG. The average final FBGs in patients who formerly took metformin for 2–6 weeks and in patients using metformin for > 6 weeks were each 162.36 ± 46.82 mg/dL and 138.90 ± 46.63 mg/dL. Meanwhile, both Css^{max} and Css^{min} insignificantly influenced final FBG (P 0.160 and P 0.126, respectively) with a moderate correlation. A finding different from the prediction was shown by the positive correlation between Css^{max} and final FBG, FBG changes, final GA, and GA changes. It was unexpected due to the various hyperglycemic baselines. Glycemic response of antidiabetics has been known to be influenced by glycemic control baseline [44]; therefore, in nearly controlled FBG, antidiabetics are administered for maintaining glycemic control. A similar finding was shown by a RCT study involving 529 newly-diagnosed T2DM patients, in which rapid FBG decrease occurred one week after metformin therapy and lasted for 8 weeks of use, and it functioned as maintenance therapy until the study ended in week 24 [46].

As expected, a correlation appeared between Css^{min} and FBG as well as FBG changes. However, this study found no influence of Css^{min} on final GA or GA changes. Meanwhile, a RCT study involving 451 T2DM patients resulted in a significant FBG reduction after administration of 1000 mg/day metformin compared to the placebo. More decrease in FBG occurred along with the increasing dose of up to 2000 mg/day [47]. In addition, glycemic response is more obvious in patients with high baseline of hyperglycemia, such as in 1856 patients of 3 RCT studies showing that the best antidiabetic response occurred to patients with HbA1c ≥ 8% [44]. The differences in average FBG baseline and involvement of patients with good glycemic control might cause the discrepancy between research findings and predicted results. A study involving 18 T2DM patients showed up to 8.1% reduced GA after metformin administration that was monitored every 4 weeks [48]. The lower response in this study, 4.85%, was caused by differences in metformin doses. Unachieved glycemic control, particularly with metformin Css^{min} (67.9% respondents) might also contribute to the metformin response in this study. The baseline GA, which was 12.65% higher than the average initial GA of this present study, had resulted in lower GA reduction.

In general, this study found that metformin Css^{max} showed an unexpected correlation with glycemic response. Besides limited number of patients, the high variations of hyperglycemic baseline caused the analysis of metformin Css^{max} to show some contradictive results. Although with weak negative correlation, Css^{min} influenced FBG. This finding confirmed the importance of calculating the dose and interval of metformin administration, such as in obese patients, to maintain Css^{min} within the recommended therapeutic range. A long-term study involving far more respondents and using equal initial hyperglycemia, completed with more-frequent assessment of glycemic control, would produce a more comprehensive analysis relating to metformin steady-state concentration and its glycemic response. After being treated with metformin 1000 mg/day, the percentage of patients with metformin Css^{min} was 32.1% while 84.1% had metformin Css^{max} within the recommended therapeutic range. Patients with metformin monotherapy possessed higher Css^{max}, but patients having a longer duration of metformin administration possessed significantly higher Css^{min}. Metformin Css^{min}, together with initial hyperglycemia, was the only factor that influenced FBG.

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Declarations of interest

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jcte.2018.05.001.

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