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Original Article

Effect of metformin and metformin-sulfonylurea on lipid profile of type 2 *diabetes mellitus* patients: A cross-sectional study

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ABSTRACT

Background and Aims: In addition to lowering blood glucose levels, metformin also has a positive effect on the lipid profile by affecting gluconeogenesis and lipogenesis in the liver. Conversely, sulfonylurea is reported to possibly worsen the lipid profile and increase the risk of cardiovascular disease. Therefore, we would like to know whether there is a significant difference in the lipid profile of type 2 diabetes mellitus patients taking metformin as monotherapy and metformin-sulfonylurea as a combination since these two medicines are very commonly used in Indonesia.

Methods: A cross-sectional study was performed on 88 patients with type 2 diabetes mellitus who were restricted on metformin or metformin-sulfonylurea for equal to or more than 1 year. Subjects on metformin (n=37) and metformin-sulfonylurea (n=51) were asked to fast for at least 8 hours before blood sampling. We measured the lipid parameters from subjects' blood samples using a standardized enzymatic method.

Results: All basic characteristics of the study subjects in these two groups were matched. We found that total cholesterol, LDL-cholesterol, and triglyceride were lower and HDL-cholesterol was higher in the metformin group than the metformin-sulfonylurea group but not statistically significant ($p>0.05$). Multivariate analysis showed no significant differences for both therapies in any parameters before and after being adjusted by confounders. Only the increase in BMI contributed significantly to the increase in triglyceride.

Conclusion: This study presents no statistical differences in lipid profile after ≥1 year consumption of metformin and metformin-sulfonylurea combination.

Keywords: *Diabetes mellitus*, Metformin, Sulfonylurea, Lipid profile

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INTRODUCTION

Diabetes mellitus occurs due to the disruption of the endocrine system, making blood glucose levels abnormal and further causing complications in the human organ system (WHO, 2021). Patients with type 2 diabetes mellitus typically have obesity and insulin resistance, which could cause metabolic syndrome and impaired lipid metabolism (Jaiswal et al., 2014; Schofield, Liu, Rao-Balakrishna, Malik, & Soran, 2016). Hyperlipidemia in patients with type 2 diabetes mellitus can lead to many comorbidities, including cardiovascular diseases (Bangert, 2008; Chapman, et al., 2011). The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) developed an overall approach for the glucose-lowering medication (antidiabetic) in type 2 diabetes mellitus (Davies et al., 2018). In this recommended algorithm, metformin is still the first-line oral antidiabetic drug. The combination of sulfonylurea and metformin is the second step in the management of patients with type 2 diabetes suggested by the ADA, EASD, and also the Indonesian Endocrinologist Association (PERKENI) (Adler, Shaw, Stokes, & Ruiz, 2009; PERKENI, 2015). Since many patients are put on both medications, an evaluation is not only needed for their capacity in lowering blood glucose levels but also their ability to prevent the progression of comorbidities (Davies et al., 2018). Metformin has been consumed by 60% of type 2 two diabetes patients worldwide due to lower long-term risk than other oral antidiabetic drugs (Berkowitz, et al., 2014). In addition to lowering blood glucose levels, metformin also affects the lipid profile of diabetes mellitus patients by affecting gluconeogenesis and lipogenesis in the liver (Brunton et al., 2005; Laisupasin, Thompat, Sukarayodhin, Sornprom, & Sudjaroen, 2013; Shaw et al., 2005). It is reported that metformin gives a positive effect to triglyceride, low-density lipoprotein cholesterol (LDL-c), and high-density lipoprotein cholesterol (HDL-c) levels after long usage (Busti, 2015). We also previously found that metformin was more effective than metformin-sulfonylurea in decreasing oxidative stress and urine albumin-to-creatinine ratio (UACR) (Sauriasari, Andriany, Sekar, & Azizahwati, 2017). In a meta-analysis reported by Rao, Kuhadiya, Reynolds, & Fonseca (2008), combination therapy of metformin and sulfonylurea significantly increased the risk of cardiovascular hospitalization or mortality, (fatal and nonfatal events) irrespective of the metformin monotherapy or sulfonylurea monotherapy. A recent cohort study also showed an increase in cardiovascular disease incidences in female patients with type 2 diabetes mellitus who use a combination of metformin and sulfonylurea for ten years (Li, Hu, Ley, Rajpathak, & Hu, 2014). Hypoglycemia, a frequent side effect due to sulfonylurea, is known as an important factor that affects cardiac performance (Middleton et al., 2017). Sulfonylureas have a small effect on lipids although they may statistically increase the level of free fatty acid (FFA) and triglyceride and decrease LDL-c and HDL-c (Chen et al., 2015). When compared to metformin, sulfonylureas could increase total cholesterol (TC) and LDL-c (Chen, et al., 2015). In this study, we would like to focus on a combination of metformin and sulfonylureas rather than sulfonylurea alone. We aimed to know whether there are significant differences between metformin-sulfonylurea compared to metformin alone on lipid profile since these two drugs are commonly prescribed in Indonesia. The study subjects were restricted to patients who use metformin or metformin-sulfonylurea for long term (≥ 1 year).

MATERIAL AND METHODS

This study was approved by The Ethics Committee, Faculty of Medicine, Universitas Indonesia - Dr. Cipto Mangunkusumo Hospital (Number:016/UN2.F1/ETIK/2018). Clinical examinations were undertaken using informed consent, and questionnaires were given to subjects before sampling takes place.

This cross-sectional study is part of the project aimed to compare metformin and metformin-sulfonylurea effectiveness by examining several clinical outcomes, including renal function (Sauriasari, Aristia, & Azizahwati, 2020) and lipid profile. We carried out the study by conducting a consecutive sampling on subjects with type 2 diabetes mellitus who were outpatients at Pasar Minggu Primary Health Care, Jakarta, Indonesia, from March to May 2018. The daily dose of metformin used by the patients was in the range of 500 mg 2-3 times daily and 850 mg 1-2 times daily. The sulfonylurea drug used by the patients in this study was is glimepiride 1-2 mg once daily. The exclusion criteria included patients over 25 years old who had been consistently taking metformin therapy or metformin-sulfonylurea therapy for at least one year before the sampling, based on the information provided in the medical record. All patients then were asked to fast for at least eight hours before the blood sampling was taken. The exclusion criteria were patients with insulin therapy and/or other oral antidiabetic drugs and patients with changes in therapy within one year of drug consumption based on data in the medical record. We calculated the minimum sample size using a calculation for mean comparison between the two groups with 5% of type 1 error (α) and 80% of the power of the test (1-β). The minimum sample size was 23 per group.

Blood samples were obtained from the patient's fingertips using a sterile lancet (General Care, Indonesia). The blood was picked by a capillary rod (Infopia, USA) to lipid profile test strip (LipidPro™ test strip, Infopia, USA) and HbA1c test cartridge (Afinion™ HbA1c Test Cartridge, Alere, USA). The blood samples were analyzed by a Lipid Profile Analyzer (LipidPro™ Testing Meter Infopia, USA) and an HbA1c analyzer (Alere Afinion™ AS100 Analyzer).

The lipid profile calculation used an analysis tool that applied the Friedewald formula. The Friedewald formula (FF) is one of the main methods for evaluating the amount of LDL-Cholesterol (LDL-C). In calculations using this formula, total cholesterol (TC), triglyceride (TG), and HDL-cholesterol (HDL-C) levels are needed. For each component, the calculations of TC, TG, and HDL-C are in units of mg/dL and not applicable for mmol/L units.

$$\text{LDL-C} = \text{TC} - \text{HDL-C} - (\text{TG}/5)$$

The data were then analyzed statistically. We selected covariates to be included in the multivariate model by conducting a bivariate analysis. Covariate that correlates with the outcomes

(Total Cholesterol, LDL, HDL, or triglyceride) with p<0.25 was included in the multivariate analysis.

RESULTS

The basic characteristics of the study subjects in the two groups were matched (Table 1). The proportion of gender, age, body weight, body height, BMI, the duration of diabetes mellitus, exercise habit, smoking habit, and the use of antihypertensive and antihyperlipidemic were not different between the two groups (p>0.05). However, the HbA1c level was significantly lower in the metformin group than the metformin-sulfonylurea group (Table 1).

Table 2 shows that patients taking metformin showed better lipid profile results than patients taking metformin-sulfonylurea, especially at the triglyceride levels, although not statistically significant. The ratio of LDL to HDL in the two study groups was more than 3:1, indicating a low HDL level (Table 2). The mean of total cholesterol level in subjects taking metformin and that of subjects taking metformin-sulfonylurea were within the normal limits (Table 2). However, the mean of HDL, triglyceride, and LDL levels in both groups were outside of the normal limits. The mean of total cholesterol, HDL, triglyceride, and LDL levels were better in the metformin group in relation compared to the metformin - sulfonylurea group although there were no significant difference (p>0.05) (Table 2). However, all parameters, except total cholesterol, were not in the normal range (Table 2).

Since there was a significant difference in the HbA1c level between the two groups, we did a stratified analysis according to the targeted HbA1c (≤7%)**.** We found better total cholesterol, LDL, HDL, and triglyceride levels in the HbA1c≤7% group although not statistically significant (Table 3).

We further conducted a multivariate analysis for each parameter. There were no significant differences in the metformin and metformin-sulfonylurea groups before and after adjusted by confounders (Table 4). Metformin-sulfonylurea showed a non-significant negative correlation with HDL and non-significant positive correlation with total cholesterol and triglyceride, even after adjusted by confounders (Table 4). However,

Table 1. Comparison of basic and clinical characteristics of the metformin group and metformin-sulfonylurea group.

Characteristic	Metformin (n=37)	Metformin–sulfonylurea (n=51)	*p*
Age (years)	64.19±7.71	61.12±7.79	0.070[a]
Gender			
Female (n)	25 (67.6)	44 (86.3)	0.065[c]
Male (n)	12 (32.4)	7 (13.7)	
Body mass index (kg/m^2)	24.30 ± 8.17	23.72 ± 4.73	0.936[b]
Duration of diabetes (years)	7.21± 5.15	8.95 ± 5.82	0.155[b]
Exercise habit (n)			
yes	24 (64.9)	28 (54.9)	0.472[c]
no	13 (35.1)	23 (45.1)	
Smoking (n)			
yes	0 (0.0)	1 (2.0)	1.000[c]
no	37 (100.0)	50 (98.0)	
Antihypertensive (n)			
yes	15 (40.5)	30 (58.8)	0.139[c]
no	22 (59.5)	21 (41.2)	
Antihyperlipidemic (n)			
yes	9 (24.3)	14 (27.5)	0.933[c]
no	28 (75.7)	37 (72.5)	
Blood Pressure			
Systolic (mmHg)	125.14±15.75	122.94±14.18	0.501[b]
Diastolic (mmHg)	76.22±5.94	77.06±6.72	0.636[b]
HbA1c (%)	7.75±1.34	9.04±1.82	**0.001[b*]**

Data presented in mean±SD or n (%); SD, standard deviation; *significant; [a]Independent T-Test; [b]Mann–Whitney Test; [c]Chi-Square Test

Table 2. Lipid profile according to the therapy groups.

	Cut-off values	Metformin (n=37)	Metformin–sulfonylurea (n=51)	*p*
Total Cholesterol (mg/dl)	<200	193.35±42.73	197.82±41.82	0.625[a]
LDL (mg/dl)	<100	125.49±40.70	125.98±44.33	0.958[a]
HDL (mg/dl)	>40	34.13±14.12	33.63±17.19	0.886[a]
Triglyceride (mg/dl)	<150	169.27±93.94	192.80±100.36	0.335[b]

Data presented in mean±SD; [a]Independent T-Test; [b]Mann–Whitney Test

Table 3. Lipid profile according to HbA1c level.

	Cut-off values	HbA1c≤7% (n=20)	HbA1c>7% (n=68)	*p*
Total Cholesterol (mg/dl)	<200	181.50±35.33	200.29±43.05	0.073[b]
LDL (mg/dl)	<100	112.75±43.11	129.60±41.99	0.120[b]
HDL (mg/dl)	>40	37.16±15.15	32.87±16.08	0.291[b]
Triglyceride (mg/dl)	<150	156.10±92.58	190.79±98.63	0.134[c]

Data presented in mean±SD; [b]Independent T-Test; [c]Mann–Whitney Test

for LDL, metformin-sulfonylurea showed a positive correlation with increased LDL but changed to a weak non-significant negative correlation after adjusted by confounders (Table 4). Additionally, only increased BMI contributed significantly to the increase in triglyceride levels (Table 4).

DISCUSSION

The distribution of female subjects dominates the total sample of each group (Table 1). Based on Indonesia Basic Health Research in 2013, the proportion of diabetes mellitus patients in Indonesia is greater in women than in men (Ministry of Health, 2013). The average BMI level in both groups did not exceed 25 kg/m^2, which was within the normal value (Nuttall F. Q, 2015). Based on data collection, gymnastic activity and daylight walk remain the most common exercise carried out frequently by the subjects. The proportion of subjects on antihypertensive and antihyperlipidemic medication did not differ significantly between the two groups. Diabetes mellitus, hypertension, and hyperlipidemia have the same clinical linkages through hyperinsulinemia (Tsimihodimos, Gonzalez-Villalpando, Meigs, & Ferrannini, 2018).

Chronic insulin resistance in diabetes mellitus patients may influence the subjects' lipid profiles. In type 2 diabetes mellitus patients, hyperinsulinemia, frequently insulin resistance, and β cell failure are related to dyslipidemia (Athyros et al., 2018). Insulin performs a role in lipolysis suppression and enhances the transport of triglycerides from blood vessels into adipose tissue for storage as well as inhibiting fatty acid oxidation. Therefore, the defect of the action of insulin on its receptors has an impact on the regulation of lipids in the body (Dimitriadis, Mitrou, Lambadiari, Maratou, & Raptis, 2011).

In this study, the total cholesterol level in both groups was still within the normal range (Table 2). It may be partially due to the use of metformin, which has an influence on lipid metabolism in the body (Kashi, Mahrooz, Kianmehr, & Alizadeh, 2016). Metformin may promote the lipid profile because of its mechanism of action in stimulating AMP-Kinase, which plays a role in liver lipogenesis (Madsen, Bozickovic, Bjune, Mellgren, & Sagen, 2015). Metformin enters the hepatocytes via Organic Cation Transporter 1(OCT1), a hepatic uptake transporter, and runs the interference of complex-1 in the mitochondria. The restrained complex-1 decreases the ATP/AMP ratio resulting in the activation of LKB1 (B1-liver kinase) and AMP-Kinase. The active AMP-Kinase phosphorylates HMG-CoA (3-hydroxy-3-methyl-glutaryl-coenzyme A) reductase, thus converting it into an inactive form (Madsen et al., 2015). HMG-CoA reductase is an enzyme that represents a role in cholesterol biosynthesis. Therefore, if a substance inhibits the action, i.e., metformin, the cholesterol level in the body will also decrease (Zhang et al., 2015).

On the other hand, a meta-analysis of randomized controlled trials (RCTs) which assess the effects of sulfonylureas, alone or in combination, showed that sulfonylurea increased the level of TC and LDL-c when compared to metformin and decreased HDL-c, which is in line with our results (Chen et al., 2015; Zhang et al., 2013). Sulfonylurea use is also reported to be potentially associated with a higher risk of cardiovascular diseases (Li et al., 2014; Middleton et al., 2017).

A study reported that apart from a reliable glycemic index, HbA1c can also be used as a predictor of dyslipidemia (Zhang et al., 2013). With further elevated HbA1c levels in diabetes mellitus patients, their lipid profile will also get worse (Zhang et al., 2013). We also found similar results in which all lipid parameters were better in HbA1c≤7% group (Table 3). Concerning the results, we also considered whether the variability of the HbA1c level resulted in bias in these study results. Therefore, we performed a multivariate analysis. However, in this study, we did not find HbA1c as a significant modifying variable (Table 4).

Table 4. Effect of therapy on lipid profile before and after controlling confounders.

Variable	R^2	Standardized coefficients (β)	*p*
Total Cholesterol			
Crude Model	0.003		
Therapy group		0.053	0.625
Adjusted Model	0.058		
Therapy group		0.025	0.822
Age (years)			0.311
Gender			0.598
Body Mass Index (BMI) (kg/m^2)			0.404
Smoking status			0.173
LDL cholesterol			
Crude Model	0.000		
Therapy group		0.006	0.958
Adjusted Model	0.051		
Therapy group		-0.073	0.531
Age (years)			0.263
HbA1c (%)			0.202
HDL cholesterol			
Crude Model	0.000		
Therapy group		-0.016	0.886
Adjusted Model	0.073		
Therapy group		-0.260	0.817
Age (years)			0.364
Gender			0.268
Body Mass Index (BMI) (kg/m^2)			0.176
Smoking status			0.640
Triglyceride			
Crude Model	0.014		
Therapy group		0.119	0.268
Adjusted Model	0.107		
Therapy group		0.046	0.689
Gender			0.161
Body Mass Index (BMI) (kg/m^2)		0.256	**0.016***
HbA1c			0.215

Therapy group is in ordinal scale (1=metformin, 2=metformin-sulfonylurea); gender is in nominal scale (0=female, 1=male); smoking status is in ordinal scale (0=not smoking, 1=smoking). The statistically significant different shown as *(p<0.05).

Optimal blood glucose control in combination therapy, such as metformin-sulfonylurea, could be maintained by the action mechanism of each drug. Metformin can lower blood glucose by inhibiting mechanisms of glucose production in the liver by suppressing gluconeogenesis, diminishing glucose uptake in the small intestine, and improving the utilization of glucose by skeletal muscle and adipose tissue. Metformin can also help strengthen cell sensitivity to insulin (Natali, A., & Ferrannini, E., 2006). The metformin mechanism is supported by sulfonylurea drugs because they can enhance insulin secretion as the hormone responsible for glucose uptake into cells that decrease blood glucose concentration (Sola et al., 2015). Blood glucose level affects the HbA1c level in the body because HbA1c describes blood glucose concentration for approximately 120 days (Hussain, A., Ali, I., Ijaz, M., & Rahim, A., 2017).

Our study subjects in the metformin-sulfonylurea group have a higher HbA1c level than the metformin group (Table 1). The results of this study were different from another study conducted on Afghani patients (Florkowski C., 2013) but similar to our previous study at the same study site (Chen et al., 2015). The cross-sectional nature of our study design and the relatively small

number of sample size are some of our limitations. However, we selected patients quite tightly, and all of the basic characteristics of the study groups were matched. Concerning compliance issues, we restricted data from the patient who uses the same medication routinely for more than one year without a switch or stop. Moreover, our study site implemented a national program, namely the Chronic Disease Management Program, to maintain adherence and monitor the clinical condition of study subjects. Nevertheless, HbA1c and some of the lipid parameters of the study subjects in the two groups did not reach the normal target, indicating the diabetes mellitus management therapy in the study site should be further evaluated.

CONCLUSION

This study presents no statistical differences in lipid profile after ≥1 year consumption of metformin and metformin-sulfonylurea combination.

Peer-review: Externally peer-reviewed.

Informed Consent: Written consent was obtained from the participants.

Author Contributions: Conception/Design of Study- R.S., A., F.S.; Data Acquisition- F.S.; Data Analysis/Interpretation- R.S., F.S.; Drafting Manuscript- F.S.; Critical Revision of Manuscript- R.S., A.; Final Approval and Accountability- R.S., A., F.S.

Ethics Committee Approval: This study has been approved by The Ethics Committee, Faculty of Medicine, Universitas Indonesia-Dr. Cipto Mangunkusumo Hospital (Number:016/UN2.F1/ETIK/2018).

Conflict of Interest: The authors have no conflict of interest to declare.

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