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The lipid profile of individuals with type 2 diabetes mellitus and the effects of metformin and metformin-sulfonylurea: a cross-sectional study

N.Sravya, Dr.Rajendraprasad, P.Surendar,Pedapalli prathyusha

Samskruti College of Pharmacy

ABSTRACT

Background and Aims: Metformin decreases blood glucose levels and improves the lipid profile via influencing the liver's gluconeogenesis and lipogenesis processes. On the other hand, sulfonylurea may contribute to an already elevated risk of cardiovascular disease by making lipid profiles worse. Given the widespread use of metformin and sulfonylurea in Indonesia, we are interested in learning if these two medications significantly alter the lipid profiles of patients with type 2 diabetes mellitus.

Methods: The 88 individuals with type 2 diabetes mellitus who were required to take metformin or metformin-sulfonylurea for at least a year were the subjects of a cross-sectional research. Fasting for at least 8 hours prior to blood sample was requested of those taking metformin (n=37) or metformin-sulfonylurea (n=51). Using a conventional enzymatic approach, we evaluated the lipid characteristics from blood samples of the individuals.

Findings: The two groups of participants were identical with respect to all baseline parameters. Although there was no statistically significant difference between the metformin and metforminsulfonylurea groups, we did find that total cholesterol, LDL-cholesterol, and triglyceride levels were lower in the metformin group and HDL-cholesterol levels were higher ($p>0.05$). Neither treatment differed significantly from the other in any parameter of the multivariate analysis, both before and after confounder adjustment. Only a rise in body mass index substantially accounted for the observed rise in triglyceride levels.

The results show that after using metformin or a combination of metformin and sulfonylurea for at least a year, there are no statistically significant changes in lipid profiles.

Metaformin, sulfonylurea, and lipid profile are terms related to diabetes mellitus.

INTRODUCTION

In humans, diabetes mellitus develops when the endocrine system is disturbed, leading to abnormal blood glucose levels and subsequent organ system problems (WHO, 2021). Insulin resistance and obesity are common in type 2 diabetes mellitus patients, which may lead to metabolic syndrome and poor lipid metabolism (Jaiswal et al., 2014; Schofield, Liu, Rao-Balakrishna, Malik, & Soran, 2016).

Numerous complications, such as cardiovascular illnesses, may develop in individuals with type 2 diabetes mellitus due to hyperlipidemia (Bangert, 2008; Chapman, et al., 2011). In order to address the issue of type 2 diabetes mellitus, the ADA and EASD collaborated to create a standardized protocol for the administration of antidiabetic medicine (Davies et al., 2018). The oral antidiabetic medication metformin is still the first-line treatment in this suggested strategy. According to the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD), and the Indonesian Endocrinologist Association (PERKENI), the second step in managing patients with type 2 diabetes is the combination of sulfonylurea and metformin (Adler, Shaw, Stokes, & Ruiz, 2009; PERKENI, 2015). It is necessary to assess their efficacy to reduce blood glucose levels and to avoid the advancement of comorbidities as many patients are given both drugs (Davies et al., 2018). Worldwide, 60% of people with type 2 diabetes use metformin because it has a reduced risk of side effects compared to other oral

antidiabetic medications (Berkowitz, et al., 2014). Metformin influences gluconeogenesis and lipogenesis in the liver, which in turn alters the lipid profile of diabetes mellitus patients (Brunton et al., 2005; Laisupasin, Thompat, Sukarayodhin, Sornprom, & Sudjaroen, 2013; Shaw et al., 2005). At the end of a lengthy course of treatment, metformin is said to improve levels of HDL-c, LDL-c, and triglycerides (Busti, 2015). Our prior research (Sauriasari, Andriany, Sekar, & Azizahwati, 2017) similarly shown that metformin was superior to metformin-sulfonylurea in reducing oxidative stress and the urine albumin-to-creatinine ratio (UACR). Regardless of whether the patient was receiving metformin monotherapy or sulfonylurea monotherapy, a meta-analysis published by Rao, Kuhadiya, Reynolds, & Fonseca (2008) found that the risk of cardiovascular hospitalization or mortality (fatal and nonfatal events) was significantly increased with combination therapy of the two drugs. Metformin and sulfonylurea users are more likely to develop cardiovascular disease over the long term, according to a new cohort research (Li, Hu, Ley, Rajpathak, & Hu, 2014). According to Middleton et al. (2017), hypoglycemia is a common adverse effect of sulfonylureas and is recognized as a significant factor influencing cardiac function.

Although sulfonylureas may statistically raise FFA and triglyceride levels while decreasing LDL-c and HDL-c, their impact on lipids is minimal (Chen et al., 2015). Sulfonylureas may raise total cholesterol (TC) and low-density lipoprotein (LDL-c) levels in comparison to metformin (Chen, et al., 2015). Rather than sulfonylureas alone, we would prefer to concentrate on metformin and sulfonylurea combinations in this research. Since both metformin and metforminsulfonylurea are widely administered in Indonesia, we wanted to discover whether the two medicines had different effects on lipid profiles.

The patients who could participate in the trial had to be on metformin or metformin-sulfonylurea for at least a year.

MATERIAL AND METHODS

Universitas Indonesia's Dr. Cipto Mangunkusumo Hospital's Ethics Committee gave its stamp of approval to this research (Number:016/UN2.F1/ETIK/2018). Before sampling took place, respondents were given questionnaires, and clinical evaluations were conducted with informed permission.

This cross-sectional research examines lipid profiles and renal function (Sauriasari, Aristia, & Azizahwati, 2020) as part of a larger investigation that aims to assess the efficacy of metformin and metformin-sulfonylurea. The research was conducted out from March to May 2018 at Pasar Minggu Primary Health Care in Jakarta, Indonesia, and it included a sequential sample of people with type 2 diabetes mellitus who were seen as outpatients. The patients consumed metformin at doses ranging from 500 mg two to three times day to 850 mg one to two times daily. Patients in this trial used glimepiride, a sulfonylurea, 1–2 mg one day. Patients who did not meet the inclusion criteria were those who were 25 years old or older and who, according to their medical records, had been taking metformin or metformin with sulfonylurea continuously for at least one year before to sampling. The next step was to have the patients fast for eight hours before to blood sample. Patients whose medical records showed a change in treatment within a year after drug intake, as well as those on insulin or other oral antidiabetic medications, were not included in the study. We determined the bare minimum of a sample size by comparing the two groups' means with a 5% margin of error (α) and 80% of the test's power (1-β). Each group required a minimum of 23 participants.

An sterile lancet (General Care, Indonesia) was used to draw blood samples from the patient's fingers. The blood was collected using a capillary rod from Infopia, USA, and then sent to a lipid profile test strip and a HbA1c test cartridge, both made by Infopia. A LipidProTM Testing Meter from Infopia, USA, and an Alere AfinionTM AS100 HbA1c Analyzer were used to test the blood samples.

The analytical method used to calculate the lipid profile employed the Friedewald formula. One of the most common ways to determine the level of low-density lipoprotein cholesterol is by the use of the Friedewald formula (FF). Triglyceride (TG), HDL-cholesterol (HDL-C), and total cholesterol (TC) values are required for computations with this formula. All of the TC, TG, and HDL-C computations are done in mg/dL numbers, not mmol/L levels.

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

Next, statistical analysis was performed on the data. After doing a bivariate analysis, we choose which factors to include in the multivariate model. Each outcome (Total Cholesterol, LDL, HDL, or triglyceride) has a corresponding covariate with a p-value less than 0.25.That were included in the analysis of variance.

RESULTS

The two groups of participants in the research were comparable with respect to their baseline characteristics (Table 1). There was no significant difference ($p>0.05$) between the two groups with respect to the following demographic variables: gender, age, height, weight, body mass index (BMI), duration of diabetes mellitus, exercise habit, smoking habit, and usage of antihypertensive and antihyperlipidemic medications. In contrast to the metforminsulfonylurea group, the metformin group had a much reduced HbA1c level (Table 1).

Although not statistically significant, individuals using metformin had superior lipid profile outcomes compared to metformin-sulfonylurea patients, particularly at triglyceride levels (Table 2). Both research groups had low HDL levels, as shown by an LDL to HDL ratio more than 3:1 (Table 2).

Table 2 shows that both the metformin-only group and the metformin-sulfonylurea group had normal mean total cholesterol levels. But both sets of numbers were much higher than what's considered healthy for HDL, triglycerides, and LDL. While there was no statistically significant difference ($p>0.05$) in total cholesterol, HDL, triglyceride, and LDL levels between the metformin and sulfonylurea groups, the metformin group did have superior results overall (Table 2). Except for total cholesterol, none of the values were within the normal range (Table 2).

A stratified analysis was conducted according to the intended HbA1c ($\leq 7\%$), as there was a notable disparity in the two groups' HbA1c levels. Table 3 shows that there was an improvement in total cholesterol, LDL, HDL, and triglyceride levels in the group with a HbA1c of 7% or below, although this improvement was not statistically significant.

Additionally, we analyzed each parameter using multivariate methods.

Table 4 shows that both the metformin and metformin-sulfonylurea groups were statistically unchanged after controlling for potential variables. Even after controlling for potential confounders, the negative association between metformin-sulfonylurea and HDL and the favorable associations with total cholesterol and triglycerides persisted (Table 4). Despite this,

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

Metformin-sulfonylurea initially exhibited a positive connection with elevated LDL levels; however, after controlling for confounding factors, this correlation transformed into a weak, non-significant negative correlation (Table 4).

Table 4 further shows that the rise in triglyceride levels was largely attributable to an increase in body mass index alone.

DISCUSSION

According to Table 1, the majority of each group's participants are female. There are more women than males with diabetes mellitus in Indonesia, according to 2013 data from Indonesia Basic Health Research (Ministry of Health, 2013). Both groups' average body mass indexes were within the normal range, coming in at less than 25 kg/m2 (Nuttall F. Q., 2015).

According to the data that was collected, the participants' most prevalent forms of exercise include daylight walks and gymnastic activities. There was no significant difference between the two groups in terms of the percentage of participants using medication to control hypertension and hyperlipidemia. According to Tsimihodimos, Gonzalez-Villalpando, Meigs, and Ferrannini (2018), hyperinsulinemia is a common clinical determinant of diabetes mellitus, hypertension, and hyperlipidemia.

Lipid profiles may be affected by chronic insulin resistance in individuals with diabetes mellitus. According to Athyros et al. (2018), dyslipidemia is associated with hyperinsulinemia, insulin resistance, and beta cell failure in individuals with type 2 diabetes mellitus. Insulin inhibits fatty acid oxidation and has a function in lipolysis suppression; it also improves the transfer of triglycerides from blood arteries into adipose tissue for storage. Therefore, the body's lipid control is affected by insulin's ineffective action on its receptors (Dimitriadis, Mitrou, Lambadiari, Maratou, & Raptis, 2011).

Both groups' total cholesterol levels remained within the normal range, as shown in Table 2. According to Kashi, Mahrooz, Kianmehr, and Alizadeh (2016), metformin affects lipid metabolism in the body, which might explain a portion of the problem. By activating AMP-Kinase, a protein involved in liver lipogenesis, metformin may improve lipid profiles (Madsen, Bozickovic, Bjune, Mellgren, & Sagen, 2015). Metformin binds to the mitochondria via the interference of complex-1 and enters the hepatocytes via the hepatic uptake transporter known as Organic Cation Transporter 1 (OCT1). Restrained complex-1 activates LKB1 (B1-liver kinase) and AMP-Kinase by lowering the ATP/AMP ratio.

An inactive version of HMG-CoA (3-hydroxy- 3-methyl-glutaryl-coenzyme A) reductase is produced when the active AMP-Kinase phosphorylates it (Madsen et al., 2015). One enzyme involved in cholesterol production is HMG-CoA reductase.

According to Zhang et al. (2015), a drop in cholesterol levels is a side effect of using metformin or another medication that inhibits the activity.

Conversely, our findings are consistent with a meta-analysis of randomized controlled trials (RCTs) that evaluate the effects of sulfonylureas, either alone or in combination. This meta-analysis found that sulfonylureas raised TC and LDL-c levels compared to metformin, while decreasing HDL-c (Chen et al., 2015; Zhang et al., 2013). According to Li et al. (2014) and Middleton et al. (2017), sulfonylurea usage may also be linked to an increased risk of cardiovascular illnesses.

According to research, HbA1c may serve as a predictor of dyslipidemia in addition to being a valid glycemic index (Zhang et al., 2013). According to Zhang et al. (2013), the lipid profile of individuals with diabetes mellitus deteriorates as their HbA1c levels continue to rise. In Table 3, we also observed comparable outcomes, where the group with HbA1c levels of 7% or below had superior lipid markers. With respect to the findings, we further thought about whether the study's conclusions were skewed due to the inherent unpredictability of the HbA1c level. For that reason, we ran a multivariate analysis. Table 4 shows that HbA1c was not a significant moderator in this research.

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).

The action mechanism of each medicine in combination treatment, such metformin-sulfonylurea, might keep blood glucose levels at an optimal level. Insulin levels may be reduced by metformin.

via reducing glucose absorption in the small intestine, enhancing glucose utilization by skeletal muscle and adipose tissue, and blocking pathways of glucose synthesis in the liver (gluconeogenesis). In addition to lowering blood sugar levels, metformin may make cells more responsive to insulin (Natali & Ferrannini, 2006). By increasing insulin production, the hormone that lowers blood glucose levels via glucose absorption into cells, sulfonylurea medications lend credence to the metformin mechanism (Sola et al., 2015). Because HbA1c represents the concentration of blood glucose for around 120 days, it is affected by blood glucose levels (Hussain, A., Ali, I., Ijaz, M., & Rahim, 2017).

According to Table 1, the HbA1c level of our research individuals who were given metformin with sulfonylurea was greater than that of the metformin group. Contrary to a prior research by Florkowski C. (2013) on Afghani patients, this one found findings that were comparable to those of our prior investigation at the same location (Chen et al., 2015). Our research has a few limitations, including a small sample size and a cross-sectional methodology. Despite this,

patients were carefully chosen, and the research groups were matched with respect to all essential features. We limited patient data from those who have taken the same drug continuously for over a year without interruption in order to address compliance concerns. Additionally, in order to keep track of the individuals' clinical status and ensure they were on track with their medication, our research site used a nationwide program called the Chronic Disease Management Program.

However, it is necessary to conduct further evaluations of the diabetic mellitus management medication at the study site since both groups' HbA1c and some lipid indicators did not meet the normal aim.

CONCLUSION

There are no statistically significant changes in lipid profile seen in this research after a year of using metformin or a combination of metformin and sulfonylurea.

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