

Analisis Risiko Penyakit Kardiovaskular pada Pasien Diabetes Melitus Tipe 2 dan Hipertensi yang Mengonsumsi Metformin

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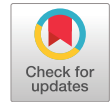


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The Analysis of Cardiovascular Disease Risk in Type 2-Diabetes Mellitus and Hypertension Patients Consuming Metformin

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Abstract

Increased blood sugar levels indicate a metabolic disease known as diabetes mellitus (DM). DM is often accompanied by hypertension. Antidiabetic therapy that can be used is metformin, either monotherapy or combined with other drugs such as glimepiride. Uncontrolled DM and hypertension will increase the risk of heart disease. This study aimed to analyze the risk of heart disease based on creatine phosphokinase (CPK) in patients with type 2 DM and hypertension who are taking metformin and a combination of metformin and glimepiride. We conducted an analytic observational using a cross-sectional design and applied a purposive sampling technique. The study subjects were type 2 DM patients with hypertension who met the inclusion criteria. The data analysis used univariate analysis, Mann-Whitney, and Fisher's. The results showed that women aged 60-75 years old with uncontrolled FBS, duration of DM < 5 years, and high CPL level were dominated by our respondents. We found that there was no difference in CPK values ($p=0.916$), and there was no relationship between the use of metformin monotherapy or the combination of metformin and glimepiride on the risk of heart disease in type 2 DM patients with hypertension ($p=0.693$). In conclusion, metformin consumption in type 2 DM patients has no significant association with heart disease risk.

Keywords: CPK, Glimepiride, Hypertension, Metformin, Type 2-diabetes mellitus

Abstrak

Peningkatan kadar gula darah merupakan salah satu gejala penyakit metabolisme yang dikenal sebagai diabetes melitus (DM). Penyakit DM seringkali disertai penyakit hipertensi. Terapi antidiabetes yang dapat digunakan yaitu metformin baik monoterapi maupun kombinasi dengan obat lainnya seperti glimepirid. DM dan hipertensi yang tidak dikontrol akan meningkatkan risiko penyakit jantung. Penelitian ini dilakukan untuk menganalisis risiko penyakit jantung berdasarkan CPK pada pasien DM tipe 2 dengan hipertensi yang mengonsumsi metformin dan kombinasi metformin dengan glimepiride. Penelitian ini merupakan penelitian observasional analitik dengan rancangan cross sectional dengan mengaplikasikan teknik purposive sampling. Subjek penelitian merupakan pasien DM tipe 2 disertai hipertensi yang memenuhi kriteria inklusi. Analisis data yang digunakan yaitu analisis univariat, uji Mann-whitney dan uji Fisher. Hasil penelitian menunjukkan wanita, usia 60-75 tahun, glukosa puasa tidak terkontrol, durasi DM < 5 tahun, dan tingginya kadar CPK mendominasi pada responden penelitian ini. Penelitian ini menemukan bahwa tidak terdapat perbedaan nilai CPK ($p=0,916$) dan tidak terdapat hubungan antara penggunaan monoterapi metformin maupun kombinasi metformin dan glimepiride terhadap risiko penyakit jantung pada pasien DM tipe 2 disertai hipertensi ($p=0,693$). Kesimpulan penelitian ini adalah konsumsi metformin pada pasien DM tipe 2 tidak memiliki hubungan yang signifikan terhadap risiko penyakit jantung.

Kata Kunci: CPK, Diabetes melitus tipe 2, Glimepirid, Hipertensi, Metformin



INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease characterized by hyperglycemia. Abnormalities of insulin production, insulin sensitivity, or both could cause DM (PERKENI, 2021). Around 90% of DM cases are dominated by type 2 DM (Goyal & Jialal, 2022). Type 2 DM occurs due to insulin resistance in muscle and adipose cells and failure to produce insulin from pancreatic beta cells (PERKENI, 2021). The International Diabetes Federation (IDF) states that 537 million adults aged 20-79 years have diabetes worldwide, and it is estimated that this figure will continue to increase every year. In 2021, as many as 6.7 million people died from diabetes mellitus, and one person died every 5 seconds (IDF, 2021). The incidence of DM in Indonesia is 1,017,290 people of all ages. The number of people living with diabetes mellitus at DI Yogyakarta is 14,602 (Kemenkes RI, 2019). Sleman Regency has the highest type 2 DM prevalence compared to other districts in Yogyakarta (Dinas Kesehatan DIY, 2020).

Research conducted by Abdissa & Kene (2020) stated that the majority of diabetic patients suffer from hypertension. Hypertension is a persistent increase in systolic blood pressure (Dipiro et al., 2015). Hypertension is estimated to occur in 1.28 billion adults aged 30-79 worldwide. However, the current management of hypertension is not optimal. WHO (2021) data showed that 46% of adults are unaware that they are suffering from hypertension. The number of adults with hypertension is 1.28 billion, and more than 700 million people do not have the treatment. As a result, only 1 in 5 adults with controlled hypertension. In addition to being a global problem, hypertension is also a problem in Indonesia. According to WHO (2021), hypertension in Indonesia has increased by 12% from 1999-2019. Indonesia ranked fourth as the country with the most significant prevalence increase globally. Riskesdas 2018 reported that the prevalence of hypertension reached 658,201 people (Kemenkes RI, 2019), while for the D. I. Yogyakarta province area of 10,038 people, and in the Sleman region it is recorded at 107,449 people (Dinas Kesehatan DIY, 2020).

The prevalence of DM accompanied by hypertension in several regions is 37.4% in Jimma, 40.45% in Pakistan, 70.4% in Morocco, 76% in Jordan, 85.6% in Benghazi, Libya, and 89.6% in Iraq. The incidence of DM accompanied by hypertension has the risk of increasing cardiovascular risk and death by 41% and 44% (Abdissa and Kene, 2020).

Type 2 DM and uncontrolled hypertension can increase the risk of complications, one of which is heart disease. This increased risk occurs due to glucotoxicity, which increases the renin-angiotensin-aldosterone system (RAAS), enhancing hypertension risk. Hypertension accompanied by increased oxidative stress and radical oxygen activity will mediate blood vessel damage due to angiotensin II activation and aggravate endothelial dysfunction, thereby increasing the risk of coronary heart disease (Yuliani et al., 2014). Therefore, patients need antidiabetic therapy to reduce the risk of these complications.

Metformin is one of the antidiabetic agents of the biguanide group and is recommended as the first-line treatment of type 2 DM. Metformin works through two main mechanisms: reducing hepatic glucose production (gluconeogenesis) and increasing peripheral glucose absorption, including skeletal muscle (Hardianto, 2021; PERKENI, 2021). Metformin could reduce cardiovascular risk (PERKENI, 2021). This statement was also supported by Han et al. (2019), who stated that metformin has a positive effect on cardiovascular protection (cardioprotective) by activating phosphorylation of adenosine monophosphate protein kinase (AMPK), which can reduce oxidative stress, reduce the production of inflammatory cytokines and increase the activity of endothelial nitric oxide synthase (eNOS). Apart from being monotherapy, metformin can also be combined with other antidiabetic groups, one of which is from the sulfonylurea group, such as glimepiride. These two drugs can be combined because they have different mechanisms of action. Glimepiride is recommended as a second-line therapy for type 2 DM while considering cost. This drug has a mechanism to increase insulin secretion in pancreatic beta cells (PERKENI,

2021). Hassan & Abd-Allah (2015) reported that the combination of metformin and glimepiride is better at controlling glycemic than the combination of metformin and gliclazide. The combination of metformin and glimepirid may also lower cardiovascular risk factors.

One of the goals of therapy for type 2 DM and hypertension is to reduce the risk of complications, including heart disease. Creatine phosphokinase (CPK) test can be used to detect heart conditions. CPK is an enzyme in muscle, brain, and heart tissue (Aujla & Patel, 2022). However, these enzymes will mainly be released into the blood circulation in conditions such as cardiac muscle necrosis and acute myocardial infarction (Jacob & Khan, 2018). Average CPK values range from 20 to 200 IU/L. Creatine kinase activity increases within 12 hours after acute myocardial infarction symptoms and peaks at 24 to 36 hours. It returns to normal after 48 to 72 hours. CK activity could elevate in chronic conditions such as rhabdomyolysis, chronic muscle disease, burns, and even after strenuous exercise. Therefore, CK-MB isoenzyme is considered a parameter for acute myocardial infarction (Aujla & Patel, 2022). This study aimed to analyze the effect of metformin (either monotherapy or combination with glimepiride) and the risk of heart disease among type 2 DM patients accompanied by hypertension based on CPK biomarkers.

METHODS

This study was an observational analytic, which applied a cross-sectional design. Before this study began, the author had applied for a research permit to the Sleman District Health Office and had obtained ethical clearance from Ethics Committee of STIKES UNRIYO(027.3/ FIKES/PL/III/2023). The study was conducted in primary health care in Sleman District, especially the Depok region. The research was done from April to August 2023.

We applied purposive sampling techniques based on inclusion criteria (diagnosed with diabetes mellitus and hypertension, BPJS participants, age range 40-75 years, consuming

metformin monotherapy or a combination of metformin and glimepiride at least six months before the study) and exclusion criteria (diagnosed with atherosclerosis cardiovascular disease (ASCVD), having a history of rhabdomyolysis, chronic muscle disease, burns and after strenuous exercise, unwilling to sign informed consent).

Statistical analysis includes univariate analysis, the Mann-Whitney test, and the Fisher Exact test. Univariate analysis was used to describe the characteristics of research respondents. The Mann-Whitney test was applied to analyze the difference in CPK values between respondents who used metformin as a monotherapy and a combination with glimepiride. The Fisher Exact test was used to determine the relationship between the use of metformin monotherapy and a combination of metformin and glimepiride on the risk of heart disease.

RESULT AND DISCUSSION

Characteristics of Respondent

This research was conducted at Depok 1 and Depok 3 primary health care in Sleman Regency, D.I. Yogyakarta, using research subjects that had been selected according to inclusion and exclusion criteria (Figure 1) with respondent characteristic data shown in Table 1. The gender of respondents is dominated by women, namely as many as 30 people (66.7%) while the number of male respondents is 15 people (33.3%). Milita et al., (2021) confirmed that women have a greater incidence of diabetes mellitus. Women tend to increase their body mass index when monthly, and postmenopausal cycle syndrome occurs, so the body fat distribution is uneven and quickly accumulates due to these hormonal changes. Therefore, it could increase DM risk (Roniawan et al., 2021).

The age data showed that 37.8% were 45-59 years old and 62.2% were 60-75. Putra et al., (2019) declared that respondents with type 2 DM are dominated by ages 60-80. The aging process may affect the ability of pancreatic cells, which reduces insulin production, changes in carbohydrate metabolism, and changes in the

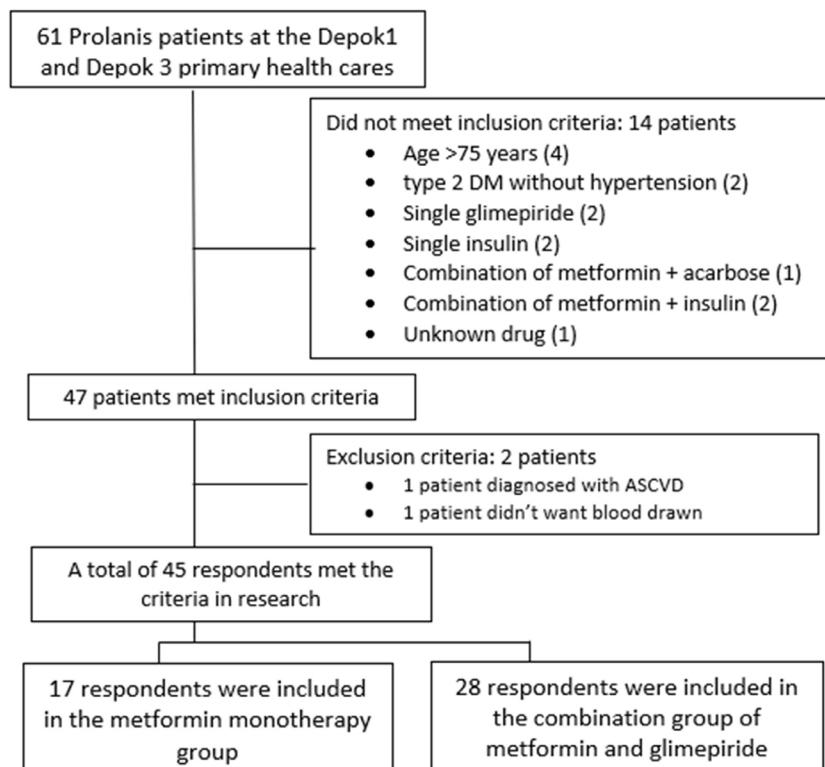


Figure 1. Respondent recruitment

release of glucose and insulin (Febriani & Fitri, 2020; Rosita et al., 2022).

The Fasting Blood Glucose (FBS) of respondents <126 mg/dL were 20 people (44.4%), and respondents with FBS \geq 126 mg/dL were 25 people (55.6%) with a mean of FBS 130.81 mg/dL (uncontrolled). The results obtained were in line with research conducted by Rumana et al. (2018), namely the average FBS in type 2 DM patients of 164.89 mg / dL (\geq 126 mg/dL). In another study conducted by Charisma (2017), which examined the FBS levels in DM patients, *Program Pengelolaan Penyakit Kronis* (PROLANIS) participants obtained results of 79% of study subjects had abnormal fasting blood sugar levels (>126 mg/dL). The increase in FBS levels in respondents was caused by changes in glucagon and insulin hormones that increase and decrease blood glucose levels (Yulia et al., 2022). Uncontrolled FBS in DM patients affects the risk of macrovascular complications due to metabolic disorders because increased blood sugar levels accelerate the formation

of atherosclerotic plaques and rupture so that they can clog large blood vessels in the heart, peripheral arteries and brain (Suryanegara et al., 2021). Based on systolic blood pressure data (SBP), it was classified as average SBP (<130 mmHg) as many as seven people (15.6%), normal-high (130-139 mmHg) as many as 12 people (26.7%), grade 1 hypertension (140-159 mmHg) as many as 16 people (35.6%) and grade 2 hypertension (\geq 160 mmHg) as many as ten people (22.2%) while for diastolic blood pressure (DBP) data classified as normal DBP (<85 mmHg) as many as 21 people (46.7%), normal-high (85-89 mmHg) as many as seven people (15.6%), grade 1 hypertension (90-99 mmHg) as many as 14 people (31.1%) and grade 2 hypertension (\geq 100 mmHg) as many as three people (6.7%).

The mean systolic and diastolic blood pressure was 143.80 mmHg and 84.84 mmHg. Putri et al. (2020) found that the mean of SBP of 154.88 mmHg (>140 mmHg) and DBP of 83.55 mmHg (<85 mmHg). Based on the criteria for controlling diabetes mellitus accompanied

Table 1. Respondent Characteristics

Characteristic	Frequency (n=45)	%	Mean \pm SD
Gender			
Male	15	33.3	-
Female	30	66.7	
Age			
45-59 years	17	37.8	60.69 \pm 5.72
60-75 years	28	62.2	
Fasting blood glucose			
<126 mg/dL	20	44.4	130.81 \pm 36.31
\geq 126 mg/dL	25	55.6	
Systolic blood pressure			
<130 mmHg	7	15.6	
130-139 mmHg	12	26.7	
140-159 mmHg	16	35.6	143.80 \pm 17.73
\geq 160 mmHg	10	22.2	
Diastolic blood pressure			
<85 mmHg	21	46.7	
85-89 mmHg	7	15.6	
90-99 mmHg	14	31.1	84.84 \pm 9.90
\geq 100 mmHg	3	6.7	
DM duration			
<5 years	38	84.4	3.22 \pm 2.10
\geq 5 years	7	15.6	
CPK (IU/L)			
20-200 IU/L	38	84.4	130.40 \pm 102.18
\geq 200 IU/L	7	15.6	

Abbreviations: DM =diabetes mellitus; CPK = creatine phosphokinase; SD = standard deviation

by hypertension, the average systolic blood pressure of respondents is categorized as uncontrolled (target <140 mmHg). In comparison, the average diastolic blood pressure of respondents has been controlled (target <90 mmHg) (PERKENI, 2021). The increase in blood pressure in diabetes mellitus patients is caused because when a person has diabetes mellitus, there is an increase in serum glucose transport so that the pancreas will be stimulated to produce more insulin. Hyperinsulinemia plays a role through increased sympathetic activation or hypertrophic stimulation of vascular smooth muscle cells, which can improve vascular pressure resistance and cause hypertension (Husni et al., 2022).

Uncontrolled blood pressure in type 2 DM could accelerate microvascular and macrovascular complications. Patients have 2-3 times higher cardiovascular mortality and an increase of 2-4 times higher risk of cardiovascular diseases such as myocardial infarction, stroke, or death compared to patients with diabetes mellitus without hypertension (Sari et al., 2017).

Data on the duration of diagnosis with diabetes mellitus was obtained on average of 3.22 years consisting of 38 people (84.4%) diagnosed for <5 years and as many as seven people (15.6%) diagnosed \geq 5 years. Roniawan et al., (2021) declared that their study was dominated by respondents with a diagnosis duration of 1-4 years, as much as 73.9% of

Table 2. Differences in CPK Values in The Metformin Monotherapy Group with a Combination of Metformin and Glimepiride

The group of diabetes mellitus therapy	CPK level	<i>p</i> value
	Mean ± SD	
Metformin monotherapy	127.59 ± 98.18	0.916
Combination metformin+glimepiride	132.14 ± 106.28	

Abbreviations:CPK = creatine phosphokinase

the total respondents. Mildawati et al. (2019) stated that longer DM duration increases the complication risk because it is caused by the buildup of blood glucose in large quantities and, over a long period, the function of organs in the body is disrupted, causing complications. Based on data from the CPK test, 38 people (84.4%) were included in the low-risk category of heart disease, and seven people (15.5%) were included in the high-risk category of heart disease with an average CPK value of 130.3 IU/L. The mean of CPK value of patients in this study was still included in the low-risk category of heart disease because <200 IU/L (Aujla & Patel, 2022). Patients with indications of heart disease will have a high CPK value, and this is due to damage that occurs in the tissue, resulting in the CPK enzyme being released into the blood vessels so that CPK enzyme levels will increase (Jacob & Khan, 2018).

Differences in CPK Values in Type 2 Diabetes Mellitus and Hypertensive Patients Using Metformin Monotherapy with a Combination of Metformin and Glimepiride

According to Table 2, the group of respondents who consumed metformin monotherapy had a mean CPK level of 127.59 IU/L. In contrast, the respondents who consumed a combination of metformin and glimepiride had a CPK level of 132.14 IU/L. There was no difference in CPK values between respondents who took metformin monotherapy and those who took a combination of metformin and glimepiride ($p = 0.916$). The average value of both groups is still classified as a low risk of heart disease because the average CPK value is <200 IU/L (Aujla and Patel, 2022).

The standard deviation (SD) value obtained is 106.276 IU/L and is quite large. In addition, in this study, several respondents had substantial CPK values, so these things caused significant data variations, as shown by large SD values.

Other factors might affect our results, including age, adherence, and DM duration. The relationship between sex and the incidence of heart disease in research conducted by Yuliani et al., (2014) states that there was a significant association between the risk of heart disease and gender ($p = 0.000$). This finding was supported by another study by Suherwin (2018) with a $p = 0.001$. When a woman has menopause, the hormone estrogen will decrease. The estrogen hormones could suppress the effect of lipase activity and contribute to lipoprotein lipase regulation. Reducing the production of the lipase hormone will have an impact on lipase activity in the liver to increase and decrease high-density lipoprotein (HDL) levels, elevating low-density lipoprotein (LDL), and improving the hydrolysis of triglycerides into chylomicrons and very low-density lipoprotein (VLDL) which causes an increased risk of heart disease (Ariadi et al., 2019).

Adherence to taking medication is one of the heart disease risk factors. The respondents of this study were elderly patients so that the schedule for blood sugar control and drug collection had been scheduled by the public health care. It was a reminder and supporting factor for patient treatment compliance. Triastuti et al. (2020) stated that in patients with diabetes mellitus, a good level of treatment adherence would reduce the risk of complications such as cardiovascular disease, nephropathy, retinopathy, neuropathy, and pedis ulcers. Nanda et al., (2018) declared that

Table 3. The Relationship Between the Use of Metformin Monotherapy and The Combination of Metformin and Glimepiride on the Risk of Heart Disease

The group of diabetes mellitus therapy	Heart disease risk		OR (95% CI)	<i>p-value</i>
	High-risk	Low-risk		
Metformin monotherapy	2	15	0.613	0.693
Combination metformin+glimepiride	5	23	(0.105-3.580)	

there was an association between adherence to taking antidiabetic drugs and blood sugar levels ($p\text{-value} = 0.015$). It is also supported by research conducted by (Romadhon et al., 2020), which obtained a relationship between the level of compliance with blood sugar tests ($p\text{-value} = 0.000$). Intensive blood sugar control in DM patients can reduce the risk of macrovascular complications (Suryanegara et al., 2021).

The mean duration of diagnosis by respondents in this study was 3.21 years (less than five years). Suciana et al., (2021) stated that there the length of suffering DM has a significant association with the incidence of coronary heart disease ($p\text{-value} = 0.017$) with a risk of 4.491 times greater in DM sufferers more than the same five years compared to DM sufferers less than five years. Yuliani et al., 2014 mentioned a similar finding related to DM duration and coronary heart disease ($p = 0.43$). The study also found that the proportion of DM patients who had coronary heart disease was 81.8% with a long period of DM >10 years and 50.8% with a long period of DM <5 years. The effect of duration DM diagnosis on the risk of heart disease is related to the formation of atherosclerotic lesions that will develop to form carotid plaques that can increase the risk of ischemic stroke (Putri et al., 2020).

We conducted CPK as an indicator of heart condition examination. CPK is a test that is often used to diagnose acute myocardial infarction. However, this examination has the disadvantage that it is not specific to the heart muscle or can show necrosis in other muscle cells (Kurniawan et al., 2016). Other tests that can be used to see the condition of the heart include CK-MB, and troponin T. CK-MB is an

isoenzyme of CPK which is mainly found in the heart muscle ($\pm 80\%$) and can reflect heart muscle damage if there is an increase in CK-MB activity. The average value of CK-MB is <24 U / L. Troponin T is a protein specific to the heart muscle. This marker is and sensitive when damaged to heart muscle cells. The advantage of this troponin examination is that it can show minor damage to the heart muscle (microscopic zone) (Prasetyo et al., 2014).

Relationship between the Use of Metformin as a Monotherapy and Combination with Glimepiride on the Heart Disease Risk in Type 2 Diabetes Mellitus accompanied by Hypertension Patients

According to Table 3, it was obtained that for the respondents who consumed metformin monotherapy, as many as 15 people were classified as low risk, and two people were classified as high risk. In the group that combined metformin and glimepiride, 23 people were classified as low risk and five people as high risk. The patients who take metformin monotherapy have a 0.613 times risk of having a high risk of heart disease compared to patients who take the combination, so metformin monotherapy affects better against the low risk of heart disease. The combination of metformin and glimepiride could increase hypoglycemia risk with moderate severity, therefore, the dose of metformin is usually lowered to reduce the risk (Poluan et al., 2020). This decrease in dose will make the resulting cardioprotective effect lower even with the addition of glimepiride because it is known that metformin has a better impact than glimepiride (sulfonylureas) in reducing cardiovascular events (Han et al., 2019).

There is no association between the use of metformin monotherapy or the combination of metformin and glimepiride on the risk of heart disease (0.693). Goldberg et al. (2022) found that the effects of metformin and placebo treatments did not reduce cardiovascular events (p -value = 0.81). Research conducted by Basnet et al. (2015), which examined the impact of metformin and non-metformin administration on myocardial infarction in people with diabetes using troponin T, CK-MB, and left ventricular ejection fraction obtained no significant relationship in metformin and non-metformin groups using the three tests with p -values of 0.56 for CK-MB examination, 0.41 for troponin T and 0.99 for left ventricular ejection fraction.

Hassan & Abd-Allah (2015) study showed the effects of several antidiabetics with a control group on cardiovascular risk factors, including FBS, plasma homocysteine, HbA1C, total cholesterol, HDL, LDL, and triglyceride. The results obtained by the combination of metformin and glimepiride are superior in reducing cardiovascular risk factors compared to the combination of metformin and gliclazide. In addition, the single metformin and the combination groups showed significant reductions in FBS, PPBS, and HbA1c results compared to the control group. The metformin group's lipid profile (total cholesterol, LDL, HDL, and triglycerides) did not provide significant changes compared to the control group. In contrast, there were substantial changes in the combination group compared to the control group, namely a decrease in total cholesterol, LDL, and triglyceride levels and an increase in HDL levels. A reduction in HbA1c levels can slow macrovascular complications. It can reduce the risk of heart attack by 14% and peripheral vascular disease by 43%, while heart disease incidence will decrease by 2-3% with a 1% decrease in total cholesterol levels (Lee et al., 2015; Supri, 2016). Regarding the decrease in HbA1c levels as an indicator of the success of diabetes mellitus therapy, there is another study conducted by Apriliany et al., (2022) which examined the effect of metformin either as monotherapy and/or as a combination

with glimepiride on HbA1c levels obtained the results that the average HbA1c levels after administration in the metformin group from 7.51 to 7.20% (a difference of 0.31%) while in the combination group the average decrease in HbA1c from 7.15 to 6.82% (difference of 0.33%) with a p -value = 0.000. The average reduction in levels in the combination group reached the target HbA1c levels in patients with DM (<7%).

The weakness of this study is that the HbA1c examination was not carried out. HbA1c examination can guide the patient's glucose control related to heart disease risk. In addition, the CPK test is often used to diagnose acute myocardial infarction, but this test is less specific to the heart muscle than other tests, such as CK-MB and troponin T.

CONCLUSION

The study concludes that there was no significant difference in CPK values between type 2 DM and hypertension patients who used metformin monotherapy with a combination of metformin and glimepiride (p -value = 0.916). There was no significant relationship between the use of metformin monotherapy and a combination of metformin and glimepiride on the risk of heart disease in patients with type 2 DM and hypertension (p -value = 0.693).

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