



Effect of Metformin Therapy on Low Density Lipoprotein (LDL) Levels in Type 2 Diabetes Mellitus Patients at Undata Hospital in Palu City Central Sulawesi

(Efek Terapi Metformin terhadap Level Low Density Lipoprotein (LDL) pada Pasien Diabetes Mellitus Tipe 2 pada RS Undata di Kota Palu Sulawesi Tengah)

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ABSTRACT

Background: Metformin, which can control blood glucose levels, can reduce LDL levels in type 2 DM patients. **Objectives:** To determine the mean value of pre and post LDL in type 2 DM patients after receiving metformin therapy for three months. **Methods:** This study used a cross-sectional study with a prospective approach, It was done by conducting pre and post examination of LDL levels using metformin. This study was analyzed using the SPSS Wilcoxon statistical test. The total sample that met the inclusion and exclusion criteria was 18 respondents. **Results:** This study used a single metformin value (sig = 0.000 <0.05) with a baseline mean value of 148.22 mg / dL and an evaluation of 133.56 mg / dL where the difference in reduction was 14.66 mg / dL. **Conclusion:** There was a decrease in LDL levels in type 2 DM patients after using metformin for three months.

Keywords: DM type 2, metformin, LDL



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ABSTRAK

Latar Belakang: Metformin yang dapat mengontrol kadar glukosa darah dapat menurunkan kadar LDL pada pasien DM tipe 2. Tujuan: Untuk mengetahui rerata nilai pre dan post LDL pada pasien DM tipe 2 setelah mendapat terapi metformin selama tiga bulan. Metode: Penelitian ini menggunakan studi potong lintang dengan pendekatan prospektif, dilakukan dengan melakukan pemeriksaan pra dan pasca pemeriksaan kadar LDL menggunakan metformin. Penelitian ini dianalisis menggunakan uji statistik SPSS Wilcoxon. Jumlah sampel yang memenuhi kriteria inklusi dan eksklusi adalah 18 responden. Hasil: Penelitian ini menggunakan nilai metformin tunggal ($\text{sig} = 0,000 < 0,05$) dengan nilai mean baseline 148,22 mg/dL dan evaluasi 133,56 mg/dL dimana selisih penurunannya adalah 14,66 mg/dL. Kesimpulan: Terjadi penurunan kadar LDL pada pasien DM tipe 2 setelah penggunaan metformin selama tiga bulan.

Keywords: DM tipe 2, metformin, LDL

INTRODUCTION

Diabetes mellitus is a condition in which the increasing glucose levels in the blood occurs when the insulin produced by the pancreas is not enough or it can also occur when the body is unable to properly use of insulin (Nuraisyah, 2017). In 2011, there were 336 million people in the world who suffered from T2DM and reached 4.6 million deaths each year. The International Diabetes Federation (IDF) states that DM sufferers will increase by 9.1 million people and become 14.1 million people in 2035. In Indonesia it is ranked 5th worldwide, in 2013 it increased by 7.6 million people. According to the Central Sulawesi Provincial Health Office, in 2015 there were 10,851 diabetes mellitus. In 2015 cases of diabetes mellitus amounted to 0.82% and increased in 2016 was 1.28%.

Metformin is an oral hypoglycemic drug widely used in type 2 diabetes mellitus. Metformin is widely used because it does not cause a boost in the insulin secretion process and cannot cause a deficiency in blood glucose. Metformin can also cause weight loss in a person. Metformin absorption occurs in the intestine and will enter the circulation but is not bound to plasma proteins; metformin is excreted in the urine without changing the form of the compounds. The half-life of metformin is about 2 hours. can use metformin because it cannot cause hypoglycemia, (Amaral et al., 2013)

Metformin induces the activation of adenosine monophosph protein kinase (AMPK) limiting the anabolic pathway and stimulating the catabolic pathway. AMPK in the heart, can inhibit sterol regulatory element-binding protein 1 (SREBP-1c) which is responsible for controlling genes needed in the lipogenesis process. This downregulation activates fatty acid desaturase (FADS), which reduces arachidonic acid levels. This reduction can lead to the increasing in membrane fluidity which functions in maintaining the function and integrity of the cell membrane, thereby increasing the recycling of low density lipoprotein cholesterol (LDL-C) receptors and reducing LDL-C levels. (van Stee, de Graaf, & Groen, 2018). In several studies, metformin monotherapy had a significant effect on reducing LDL levels. This is evidenced by research conducted by Lin et al., (2018) where metformin can reduce LDL levels in patients with type 2 diabetes mellitus. With the paired test analysis, the LDL levels were obtained, namely the initial LDL level of 111 mg/dL to 102 mg/ dL. So it can be concluded that metformin has a significant effect on LDL levels.

In 2018, the Hospital in Palu has the number of patients with type 2 diabetes mellitus of 970 people with 426 people using metformin alone or in combination. So, the usage of metformin at the Undata Hospital Palu reached 43.9% or around 44%. Therefore, it is interested to know the effect of metformin on LDL levels in patients with type 2 diabetes mellitus a hospital in Palu, Central Sulawesi.

METHODS

Prior to conducting the research, a request for Etchical Clearance was submitted to the Health Research Ethics Commission (HREC), Faculty of Medicine, Tadulako University and has been appointed with the number 6084/UN 28.1.30/KL/2020. All research subjects were asked for their

consent to be included in the study in the form of written informed consent. Before giving approval to the prospective research subject, they are given an explanation of the objectives, benefits, and research procedures. The identity of research subjects is kept confidential and is not published without the permission of the research subjects. All costs related to research are borne by the researcher.

This research is observational with analytical. The Research design was a cross sectional study which was conducted prospectively. This research was conducted at the Cardiac Center of the Hospital in Palu, Central Sulawesi. The research took place in the period of January-April 2020. The populations of this study were all patients with type 2 diabetes mellitus undergoing outpatient treatment a hospital in Palu, Central Sulawesi. The samples of this study were type 2 diabetes mellitus patients who met the inclusion criteria, namely those who received metformin treatment at a Hospital in palu and excluded patients, namely patients who did not want to continue the research, the patients died and patients taking hypolipidemic drugs. In this study, patients with a low level of education were patients who only studied up to primary school and junior high school, and in the moderate criteria patients who studied up to senior high school or vocational school, while patients who had higher education were patients who went to university. The method of taking blood patient is insert the cholesterol strip into the meter lipid pro and press the button ON. The on the meter lipid pro screen will blink when the meter is ready for the blood. Clean finger to be lancep with an alcohol swab. Prick patient finger with a lancing divide then take blood it using a blood draw stick. then put the blood sample to the test area of the strip until you hear a beep sound.test result appears in 2 minutes. The sampling technique used in this study was purposive sampling technique met the inclusion criteria in and the sampling in this study was for 3 months using a lipid pro.

Data Analysis

Data analysis using univariate method for patient characteristics and the bivariate analysis method to see the relationship between the independent variables and the dependent variable studied and the Wilcoxon non-parametric statistical test was carried out to see changes in Low Density Lipoprotein (LDL) levels before and after using metformin.

RESULTS AND DISCUSSION

Sample

The total sample obtained in research conducted a Hospital in Palu, Central Sulawesi province, amounted to 18 patients who used a single metformin. This study is limited by the presence of the COVID-19 pandemic which resulted in the sample being used with 18 patients.

Demographic Characteristics

Table 1 Demographic characteristics of type 2 Diabetes Mellitus patients

Patient Characteristics	Patients (n = 18)	Percentage (%)
Age		
<45 years	1	5,6
≥ 45 years	17	94.4
Gender		
Male	4	22.2
Women	14	77.8
Level of Education		
Low (Primary school, Junior high school)	13	72.2
Medium (Senior High School, Vocational School)	2	11.1
Higher (University)	3	16.7

Profession		
Farmer	1	5,6
Housewife	7	38.9
Entrepreneur	5	27.8
Retired	5	27.8

In table 1, Demographic characteristics of type 2 Diabetes Mellitus patients a hospital in Palu Central Sulawesi Province in 2020 It was obtained data that patients with Type 2 Diabetes Mellitus were more common in the age group ≥ 45 years, namely 17 respondents (94.4%). In research conducted by (Trisnawati & Setyorogo, 2013) found that the age group that suffered from diabetes mellitus a lot was ≥ 45 years, namely 24 respondents (75.0%). The increase in diabetes occurs with increasing age which begins with an increase in glucose intolerance. The aging process reduces the ability of pancreatic beta cells to produce insulin. In addition, in older people there was a 35% decrease in mitochondrial activity in muscle cells, this is associated with increased levels of fat in muscle which lead to insulin resistance. On research(Isnaini & Ratnasari, 2018) that with increasing age each individual can affect the decline in all body systems, one of which is the endocrine system which causes insulin resistance conditions which results in unstable blood sugar levels so that there is a relationship between age factors and the incidence of diabetes mellitus.

Research based on gender in diabetes mellitus patients at Undata Hospital, Central Sulawesi province, found that seven respondents (77.8%) were female. According to research (Isnaini & Ratnasari, 2018), as many as 40 respondents (75.5%) showed that women are more at risk of diabetes mellitus than men due to hormonal and metabolic factors. Women experiencing menopause contribute to the distribution of the increased amount of body fat accumulated very quickly due to this process, so women are more at risk of developing type 2 diabetes. Along with increasing age in women so that they experience menopause which can cause a decrease in the hormone estrogen, where the hormone estrogen plays a role in maintaining blood glucose balance. One of the factors that cause type 2 diabetes mellitus is obesity. Physically, women have a greater chance of obesity than men, because obese women cause insulin sensitivity so that blood glucose will accumulate in the form of fat in the body.

Patient characteristics based on education level were mostly in the low education category 72.2% (13 patients). This research shows that in the low category, more respondents are affected by DM than the higher education level category, because people with low education have little knowledge, so there are still many who have not maintained their diet, exercise, and awareness about maintaining health compared to respondents. who have a higher education category which will usually have a lot of knowledge in preventing disease. Research conducted by(Trisnawati & Setyorogo, 2013) shows the same results, namely low category respondents who are at risk of type 2 diabetes mellitus with 19 respondents (67.9%). According to research (Wahyu, 2017) that education is related to knowledge, because it is through the level of education that we can learn the process of achieving quality of life, especially in health.

Based on the occupational category, it was found that patients with the status of housewives experienced more diabetes, namely 38.9% (7 patients), according to the study. (Isnaini & Ratnasari, 2018)that most respondents as housewife and all women. Work as a housewife includes light physical activity and has erratic work time, if humans rarely exercise, the food substances that enter the body are not burned but are stored in the body in the form of fat and glucose, if insulin is not enough to convert glucose into energy then this is what causes type 2 diabetes mellitus. When physically active, glucose can be converted into energy. when doing physical activity will increase insulin so that glucose levels in the blood decrease. Research (Agustina, Diani, & Agianto, 2017) Housewives have a high risk of developing DM because of a lack of healthy lifestyle, lack of knowledge about diabetes, poor adherence to diabetes treatment, and rarely do physical activities or exercise.

Clinical Manifestations

Table 2. Manifestations of Type 2 DM patients.

Clinical Manifestations	Number of Patients (n = 18)	Percentage (%)
Dizzy	9	50%
Fatigue	4	22.2%
Headache	3	16.7%
Leg cramps	1	5.6%
Blurry eyes	2	11.1%

This study obtained clinical manifestations in type 2 DM patients with complaints of dizziness, there were nine respondents (50%), according to research conducted by (Insiyah & Hastuti, 2016) that the symptoms often experienced by respondents were dizziness, weakness even though they did not do heavy work, blurred vision, fatigue, headache and tingling in the legs. Feeling dizzy in type 2 DM patients is caused by changes in blood sugar levels, if the amount of blood glucose levels fluctuates a lot, the more likely a person is experiencing dizziness(Alfiah Kusuma Wardani, 2014).

Complementary Diseases

Table 3 Comorbidities for type 2 DM patients.

Complementary Diseases	Number (n = 18)	Percentage (%)
Coronary heart	13	72.2%
Osteoarthritis	2	11.1%
Enlarged prostate	1	5.6%
Immune disorders	3	16.7%
Heart failure	2	11.1%
Dyspepsia	3	16.7%

Table 3 shows that 13 patients (72.2%) were diagnosed with coronary heart disease. According to research conducted by (Idrus, 2019) that most of the patients with diabetes mellitus had heart disease by 73.4% of respondents. Increased blood glucose levels in the body that exceed normal limits in diabetes mellitus cause various cardiovascular diseases such as coronary heart disease, blockage of peripheral blood vessels.(Agustina et al., 2017). Diabetes mellitus patients have increased blood glucose levels as a result of which blood viscosity can also be increased, making the heart work harder to pump blood throughout the body. Increased glucose in the blood also causes fat levels to increase and stick to the walls of blood vessels. This sticking fat causes constriction of the blood vessels so that blood flow is interrupted, the attached fat can also cause blood vessels to become hard or a buildup of fatty plaque and blockage of blood vessels that causes narrowing of blood flow to the heart, this event is called atherosclerosis (Utami & Azam, 2019).

Treatment Profile

Table 4 Treatment therapy given to type 2 diabetes mellitus patients

Medicines	Number of Patients (n = 18)	Percentage (%)
Metformin	18	100%
Vitamin B1,B6,B12	4	22.2%
Flunarizine HCL	1	5.6%

Meloxicam	2	11.1%
Clopidogrel bisulfat	3	16.7%
Diclofenac Sodium	1	5.6%
Bisoprolol fumarate	1	5.6%
Asetilsalisilat	4	22.2%
Nitrogliserin	1	5.6%
bisoprolol	7	38.9%
Isosorbid dinitrat	2	11.1%
Lansoprasol	1	5.6%
Omeprazole	1	5.6%
Candesartan cilexetil	1	5.6%

Based on research conducted on patients with type 2 diabetes mellitus at Undata Hospital, Central Sulawesi Province, 18 people (100%) found the drug that was widely used, it is the biguanid group, the drug metformin. According to (Jonathan, K. et al, 2019) 25 patients (21.7%) used metformin alone in Bandung City Hospital. Metformin is the first-line therapy in type 2 DM patients which has the main effect of reducing gluconeogenesis and improving glucose uptake in peripheral tissues by 10-40%. In addition, metformin can also reduce lipid profiles.

Metformin, which is a biguanid drug class that works to improve insulin sensitivity, inhibits glucose formation in the liver, and suppresses appetite (almasdy, et al, 2015). Metformin is a widely used diabetes therapy. However, metformin itself often causes reactions in the form of drug side effects such as gastrointestinal disturbances, diarrhea, nausea, vomiting, flatulence. Risk factors that arise without food intake and other influencing factors, namely factors of how to take medication, drug dose of metformin and patient age (Jonathan, K. et al, 2019).

Metformin used in diabetes mellitus patients is a dose of 500 mg / day and is used twice a day for initial use for 1 week, can be increased according to the patient's condition. The daily dose of metformin is 2000 mg / day, given after meals. Research conducted by (Porter et al., 2014) in a Pekanbaru hospital that metformin 500 mg was used by respondents 2x a day with a daily dose of 1000-1500 mg / day with 53 respondents (55.2%). Research (Almasdy et al., 2015) that metformin can reduce LDL (Low Density Lipoprotein) levels.

Evaluation of LDL (Low Density Lipoprotein) Levels

Table 4 Value before and after levels of LDL using a single metformin in patients with type 2 diabetes mellitus

Evaluation Parameters (LDL)	Average (n = 18)		Difference	P Value
	Baseline	Evaluation		
Metformin single	148.22	133.56	14.66	.000 *

The results of the evaluation of LDL levels using a single metformin in table 4.8 showed an average baseline LDL of 148.22 mg / dl and a decrease in evaluation was 133.56 mg / dl. Significant reduction in LDL levels in patients receiving metformin single at a P value ($0.000 < 0.05$). Research result (Lin et al., 2018) There were 155 respondents with type 2 diabetes mellitus, LDL levels decreased significantly (< 0.001), the initial LDL level was 111 mg / dl and the final LDL level was 102 mg / dl and metformin could reduce LDL levels by 9% whereas in this study metformin reduce LDL levels by 14.66% this is because the number of samples used is different.

Research conducted by (Sugiarto et al., 2018) that metformin can also reduce LDL by ($P=0.012 < 0.05$), Metformin which can affect lipid metabolism in T2DM patients. Metformin induces activation of AMPK (Adenosine Monophosphate Protein Kinase) which regulates the energy changes that work

by limiting the anabolic pathway (the process of forming simple compounds into complex compounds) and stimulating the catabolic pathway (the process of breaking down complex compounds into simple compounds). AMPK in the liver can inhibit SREBP-1c (Sterol Regulatory Element-Binding Protein 1) responsible for controlling the genes needed in the lipogenesis process. The SREBP-1c gene was also found to be regulated by metformin. This downregulation activates FADS (fatty acid desaturase), which reduces arachidonic acid levels. Arachidonic acid is present in the membranes of body cells and is abundant in the brain, muscles and liver. This reduction can lead to an increase in membrane fluidity which functions in maintaining the function and integrity of the cell membrane, thereby increasing the recycling of LDL-C receptors and reducing LDL-C levels. (van Stee et al., 2018).

CONCLUSION

The conclusion of this study is that LDL levels before using metformin were 148.22 mg/dl after using metformin alone for three months, LDL levels decreased significantly, namely LDL levels to 133.56 mg/dl with *P* value ($\text{sig} = 0.000 < 0, 05$).

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest

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