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THE EFFECT OF ANTI-DIABETIC DRUGS REGIMEN COMBINATION WITH METFORMIN COMPARED WITHOUT METFORMIN TO CONVERSION OF ACID-FAST BACILLUS SPUTUM SMEAR IN NEW CASE OF PULMONARYTUBERCULOSIS PATIENTS AND TYPE 2 DIABETES MELLITUS

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ABSTRACT

Background : This study aims to determine the effect of a combination regimen of metformin and without metforminon the conversion of sputum smear in new cases of pulmonary TB patients with type 2 DM.

Materials andMethods: This cross-sectional study was conducted at Wahidin Sudirohusodo Hospital, Makassar Center for Lung Health, Kasi-Kasi, and Sudiang Community Health Center from August 2019. This study involved 83 new cases of pulmonary TB subjects with T2DM. New cases of pulmonary TB patients were obtained by examining AFB sputum in DM patients who had symptoms of pulmonary TB and had no history of suffering or receiving previous anti-TB drug therapy.Pulmonary TB patients receive category 1 anti-TB drugs andDM subjects were divided into 2 groups is metformin and non-metformin. Then, smear sputum is examined in the 2-month intensive phase of anti-TB drug therapy to assess the conversion of AFB sputum.

Results: From a total of 83 new cases of pulmonary TB and T2DM, 44 subjects received a combination regimen of metformin and 39 subjects non-metformin. In this study, there were 42 (95.5%) subjects who conversion sputum smear in the metformin group more higher than in the non-metformin group but statistically it was not significant (p = 0.282).

Conclusion: There was no significant relationship between the metformin and non-metformin groups on the conversion of AFB sputum smear in new cases of pulmonary TB patients and T2DM.

Keywords: Tuberculosis, Diabetes Mellitus, Metformin, Sputum Smear Conversion.

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia due to defects in insulin secretion, insulin action or both.[1] DM is a serious long-term condition with amajor impact in the lives and well-being of individuals, families and communities around the

world. Aging, changes in lifestyle, socioeconomic factors, and population growth have led to an increase in the prevalence of DM, especially type 2 DM.[2] The International Diabetes Federation (IDF) organization globally estimates that DM sufferers will increase to reach 578 million in 2030 and 700 million in 2045. Prevalence DM in Indonesia is around 10.7 million and is in the 7th position out of 10 countries with the highest number of DM sufferers in the world. In 2012, there was a prevalence of about 15% or 1.04 million people from the DM population who suffered from pulmonary TB.[3] The relationship between DM and TB has long

been known where the first report was documented by Avicenna (980-1027 AD) more than a thousand years ago but studies in the last 10-15 years have shown that DM as a risk factor for TB.[2,3] The increased risk of TB transmission in DM patients is two to three times, especially inpatients with positive acid fast bacillus (AFB).[4] The pathophysiological mechanism of the effect of DM as apredisposing risk factor for TB is chronic hyperglycemia causing cellular immune systemdepression, alveolar macrophage dysfunction, low levels of IFN-γ,pulmonary microangiopathy and micronutrient deficiency.[2]

In DM with TB, the priority of treatment is to treat TB while at the same time keeping blood glucose levels under control.[5,6] From a recent study, it was explained that metformin is the first choice in TB patients with DM because of the low risk of hypoglycemia, its effectiveness, low cost, the effect of minimal clinically relevant interactions with rifampin and

its own efficacy in providing a strong protective effect against TB.[7] It was reported that metformin independently can increase specific immunity in TB patients, reduce inflammation and increase the efficacy of TB treatment.[8] Some of the roles of metformin in TB therapy are controlling the secretion of IL-10 thus altering the host immune response. IL-10 itself works to inhibit the response of CD4 + T cells by inhibiting the function of APC cells infected with microbacteria. IL-10 also plays an important role in metabolic disorders such as diabetes because of its effect on insulin sensitivityby increase peripheral glucose uptake.Metformin therapy can be considered as anew strategy in increasing anti-TB efficacy because of its ability to control IL-10 secretion soas to alter the host immune response to TB infection and its ability to influence insulinsensitivity.[9,10] Metformin also inhibits complex-I function which can also inhibits NDH-I as apotential candidate for antibiotics against TB.[11,12] In addition, metformin acts as an activatorof Adenosine Monophosphate-Activated Protein Kinase (AMPK) in modulating the immunesystem and another role for metformin is to inhibit the growth of mycobacteria by inducingtheproduction of mitochondrial reactive oxygen species (mROS).[13,14]

In research by Ye-Jin Lee et al (2018) and Novita et al (2018)found that the metformin combination anti diabetic drugs (ADD) group hadAFB sputum smear conversion was higher than the non- metformin combination group.[15,16]

MATERIALS AND METHOD

This cross sectional study was conducted at Wahidin Sudirohusodo Hospital, Makassar Center for Lung Health, Kasi-Kasi, and Sudiang Community Health Center from August 2019. This study involved 83 new cases of pulmonary TBsubjects with DM. The research variables were age, sex, BMI, chest radiograph lesions, initialsputum smear load of AFB and conversion of the sputum smear at the end of the 2nd month ofintensive therapy where all these variables were subjects who received the metformin and nonmetformin combination regimen.

Subjects included in the inclusion criteria were male and female, aged ≥ 18 years, bacteriological diagnosis of new pulmonary TB and laboratory-confirmed DM. Subjects included in the exclusion criteria were tuberculosis patients who had relapsed, failed treatment

or resistant multidrugs (MDR-TB). Diagnosis of pulmonary tuberculosis is defined when the sputum smear examination shows M.tb (*Mycobacterium Tuberculosis*) with bacterial load + 1 / + 2 / + 3. The diagnosis of DM is based on fasting blood glucose levels ≥ 126 mg / dL, current

blood glucose ≥ 200 mg / dl, HbA1c ≥ 6.5%. The metformin combination regimen is defined as metformin in combination with other anti-diabetic drugs it is other ADD (glimepiride) and insulin. Total daily dose of metformin 1000-1500 mg / day. Combination regimens without metformin are defined as other anti-diabetic drugs not combined with metformin it is the combination of other ADD (glimepiride) and insulin or insulin alone. Body mass index (BMI)

<18.5 kg / m_2 it is underrweight, BMI 18.5-22.9 kg / m_2 it is normoweight, and BMI ≥ 23.0 kg

/ m_2 it is overweight. Minimal lesion chest X-ray is defined when the pulmonary tuberculosis process affects a portion of one or two lungs with an area no more than between the 2 front ribs

(the volume of the lung that lies above the chondrosternal junction of the second rib and the spinous processes of the IV thoracic vertebrae or the corpus of the V thoracic vertebrae) and no cavities were found. Extensive chest X-ray lesions is defined when the disease process was

broader than the minimal lesions.

This research provides the ethical requirements of the Human Biomedical Research Commission, Hasanuddin University Medical Faculty No: 607 / UN4.6.4.5.31 / PP36 / 2020. Data analysis was performed using SPSS version 26 (IBM Corp, Armonk, New York, USA). The statistical test used was the Chi Square test and the Fisher Exact test to assess the relationship between variables. The statistical test results were considered significant if the P value was <0.05.

RESULTS

In this study, a total of 83 new cases of pulmonary TB subjects with DM were obtained, of which 44 subjects received a combination regimen of metformin and 39 subjects who received a combination regimen without metformin.The sputum smear was checked twice it is before the intensive therapyand the end of the 2nd month of intensive therapy. From a total

of 83 subjects, it was found thatthe conversion of AFB sputum smear was more than 77 (92.8%) subjects and 6 (7.2%)subjects who did not have conversion (Table 1).

Table 1. Distribution of Research Variable Categories (n = 83)

Variabel		n	%
SEX	Male	48	57.8
	Female	35	42.2
AGE	≥ 40 y.o	78	94.0
	< 40 y.o	5	6.0
BMI	Underweight	9	11.7
	Normoweight	49	63.6
	Overweight	19	24.7
Lesion Chest X-ray	Minimal	11	13.3
	Extensive	72	86.7
Initial smear load of AFB	+1	56	67.5
	+2	17	20.5
	+3	10	12.0
Combination Type Anti Diabetic Drugs	Metformin	44	53.0
	Non metformin	39	47.0
Combination Type Anti Diabetic Drugs	Yes	77	92.8
	No	**6**	**7.2**

This study found that the metformin group had 42 (95.5%) more conversions of sputum smear compared to 35 (89.7%) in the non-metformin group. However, statistically there was no significant relationship between metformin and non-metformin groups with AFB sputum smear conversion with p>0.05. (Table 5.2)

Table 2 Relationship between Metformin and Without Meetformin with BTA conversion

Combination Type Anti Diabetic Drugs		Conversion		Total	P value
		Yes	No		
Metformin	N	42	2	44	p= 0,282
	%	95,5%	4,5%	100,0%	
Non metformin	N	35	4	39	
	%	89,7%	10,3%	100,0%	
Total	N	77	6	83	
	%	92,8%	7,2%	100,0%	

Table 3 shows the higher conversion of AFB sputum smears in the metformin combination regimen group on the study variables are gender, age, BMI less and more, chest x-ray lesions and initial grading of AFB sputum smear + 1. Meanwhile, in the combination regimen group

without metformin, the highest conversion of BTA sputum smears occurred in the study variables are normal BMI, initial grading of BTA+2 and BTA+3 sputum smear. However, there was no statistically significant relationship between the combination regimen of metformin and without metformin groups with conversion of AFB sputum smear according to the study variables (p>0.05).

Table 3. The Relationship Between Combination Regimens With Metformin and Without Metformin with Conversion of Sputum Smear According to Research Variables.

Variables	Combination Regiment		Conversion		Total	P value
			Yes	No		
Sex						
Male	Metformin	n (%)	21 (95.5)	1 (4.5)	22 (100.0)	0.564
	Non Metformin	n (%)	24 (92.3)	2 (7.7)	26 (100.0)	
Female	Metformin	n (%)	21 (95.5)	1 (4.5)	22 (100.0)	0.306
	Non Metformin	n (%)	11 (84.6)	2 (8.6)	13 (100.0)	
Age						
≥ 40 y.o	Metformin	n (%)	41 (95.3)	2 (4.7)	43 (84.6)	0.652
	Non Metformin	n (%)	32 (91.4)	3 (8.6)	35 (100.0)	
< 40 y.o	Metformin	n (%)	1 (100.0)	0 (0.0)	1 (100.0)	1.000
	Non Metformin	n (%)	3 (80.0)	1 (20.0)	4 (100.0)	
BMI						
Underweight	Metformin	n (%)	3 (100.0)	0 (0.0)	3 (100.0)	0.417
	Non Metformin	n (%)	4 (66.7)	2 (33.)	6 (100.0)	
Normoweight	Metformin	n (%)	20 (90.9)	2 (9.1)	22 (100.0)	0.613
	Non Metformin	n (%)	25 (92.6)	2 (7.4)	27 (100.0)	
Overweight	Metformin	n (%)	15(100.0)	0 (0.0)	15 (100.0)	P*
	Non Metformin	n (%)	4 (100.0)	0 (0.0)	4 (100.0)	
Chest X-ray						
Minimal lesions	Metformin	n (%)	8 (100.0)	0 (0.0)	8 (100.0	0.273
	Non-Metformin	n (%)	2 (66.7)	1 (33.3)	3 (100.0)	
Extensive lesions	Metformin	n (%)	34 (94.4)	2 (5.6)	36 (100.0)	0.500
	Non-Metformin	n (%)	33 (91.7)	3 (8.3)	36 (100.0)	
Initial smear load of AFB						
+1	Metformin	n (%)	32 (97.0)	1 (3.0)	33 (100.0)	0.365
	Non-Metformin	n (%)	21 (91.3)	2 (8.7)	23 (100.0)	
+2	Metformin	n (%)	7 (87.5)	1 (12.5)	8 (100.0)	0.471
	Non-Metformin	n (%)	9 (100.0)	0 (0.0)	9 (100.0)	
+3	Metformin	n (%)	2 (66.7)	1 (33.3)	3 (100.0)	0.533
	Non-Metformin	n (%)	6 (85.7)	1 (14.3)	7 (100.0)	

P*: can't be tested

DISCUSSION

The priority of treatment in DM with TB is to treat TB while at the same time keeping blood glucose levels under control.[5,6] The first choice of oral ADD therapy in DM patients with TB is metformin. DM.[15] Thus, the goal of TB treatment with DM is achieved is the conversion of smear sputum AFB after completion of intensive therapy at the end of the 2nd month.[17] In this study, it was found that the age of ≥ 40 years and male gender had the most TBwith DM compared to age <40 years and women. It is known that age ≥ 40 years is

theprevalence of the peak age at diagnosis of T2DM which has an average age range between 45-60 years.[18]Workneh et al. (2017) identified that the comorbidity of TB with DM increases with age.[19] The higher prevalence of TB with DM in men is most often due to tobacco smoking
and alcohol consumption so that more access to health centers than women. In addition, normal
BMI is also the most common, almost the same as Tripti et al (2017).[20] Nutritional factors are a risk factor for TB infection and are associated with malnutrition and DM.[20] From the results of the chest radiograph and Initial sputum smear load of AFB, it was found that the most extensive lesions of the chest X-ray and sputum smear of AFB +1. This is the same as Layali et al (2019).[22] But it is different from Barreda et al (2020) who got he most sputum smear of AFB +2 /+3.[23] This occurs because of a decrease in the immune system and a defect in alveolar
macrophages or T lymphocytes resulting in an increase in the number of bacteria in the sputum
and greater expansion of the lesion chest x-ray in TB with DM.[24] There was no statistically significant relationship between the combination regimen with metformin and without metformin with the conversion of sputum smear AFB by sex, age, BMI, chest X-ray lesions and initial grading of sputum smear AFB.This study found no significant relationship between the combination regimen withmetformin and without metformin with conversion of sputum smear AFB ($p>0.05$), it is different from Novita et al (2017) and Al-Shaer et al (2018)who get a significant relationship, but in we study the metformin combination regimen had a higher smear conversion of sputum AFB (95.5%) similar withNovita et al (2017) and Al-Shaer et al (2018).[16,.25] As it is known,metformin has an effect on TB infection, which is to suppress the growth of AMPK-dependentintracellular TB germs which facilitate lysosomal phagocyte fusion in cells infected with TBgerms such as in a pilot retrospective cohort study by Singhal et al.(2014) in Singapore.[26]According to Lee YJ et al (2017) metformin can be an adjunct to anti-TB drugs to increaseconversion of AFB sputum smear after intensive therapy at the end of 2nd month whilemetformin is widely used as the first choice oral ADD in DM patients.[14,26]

CONCLUSION

TB with DMsubjects who received metformin had more smear sputum smear conversion than subjects without metformin.

CONFLICT OF INTEREST

There are no Ethical or Financial issues, Conflicts of interests, or animal experiments related to this research.

IRB INFORMATION

This research provides the ethical requirements of the Human Biomedical Research Commission, Hasanuddin University Medical Faculty No: 607 / UN4.6.4.5.31 / PP36 / 2020.

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