The Relationship Between Glycemic Control and Length of Treatment in Tuberculosis Patients with Diabetes Mellitus

Ika Dyah Kurniati[1], Prihatin Iman Nugroho[2], Jalu Panjongko[3], Raihan Diki Ramadhanela[4]

[1,2,3,4]Universitas Muhammadiyah Semarang, Semarang, Central Java 50273, Indonesia
ika@unimus.ac.id

Abstract. Comorbidity between diabetic mellitus (DM) and tuberculosis (TB) can raise the incidence of the other. Uncontrolled diabetes mellitus (plasma HbA1C level > 7.0%) and five additional risk factors were discovered to have an impact on the failure of TB treatment. This study aims to identify the relationship between glycemic control and the length of treatment in patients with tuberculosis and diabetes mellitus. This type of research is analytical observational research with a cross-sectional design. This study used a total sampling, namely where all members of the population were sampled, a total of 31 TB patients with DM from December 2019 technique to August 2023 who met the inclusion criteria. The tools used in this research are medical record data and blood lab results (HbA1c). Bivariate analysis was carried out using the chi square test with significance $\alpha = 0.05$. The result of this research showed that the majority of TB-DM patient was male as 17 samples (54.8%). Most of the sample aged were > 50 years old as many as 22 samples (71.0%), 26 samples had HbA1c levels ≥ 7%, and the majority TB treatment duration ≤ 6 months were 18 samples (58.06%). The results of the chi-square test show p-value = 0.083 p (>0.05), meaning that there is no significant relationship between glycemic control and the length of treatment for TB-DM patients. The conclusion is glycemic control and treatment duration for TB-DM patients do not significantly correlate.

Keywords: Glycemic Control, HbA1c, Tuberculosis, Diabetes Mellitus.

1. Introduction

Comorbidity between diabetic mellitus (DM) and tuberculosis (TB) poses a danger to the treatment and prevention of TB disease globally. Ten million new instances of active tuberculosis (TB) infection are reported each year, and TB is believed to be the cause of almost 1.2 million fatalities globally. Clinicians have seen a connection between TB and diabetic mellitus (DM) for many years [1].

According to studies, DM can treble the risk of having TB and that each can raise the incidence of the other [2]. Studies have linked uncontrolled diabetes (plasma HbA1C level >7.0%) to subpar TB treatment results or possibly treatment failure. Indonesia has a

G. Setya Ayu Putri et al. (eds.), *Proceedings of the 2nd Lawang Sewu International Symposium on Health Sciences: Medical Laboratory Technology (LSISHS-MLT 2023)*, Advances in Biological Sciences Research 40,
https://doi.org/10.2991/978-94-6463-457-0_12

significant TB and DM burden. WHO report from 2020 said that Indonesia was responsible for the second-highest percentage (8.5%) of global TB incidence [3]. Given Indonesia's vast population and prevalence of DM, over 6% of adults in the country between the ages of 20 and 79 have the disease [4]. In Indonesia, individuals with pulmonary TB had an age-standardized prevalence of diabetes mellitus of 11.3%, according to a recent study [5]. Over 13% of DM patients in Indonesia between 2013 and 2016 were found to have ever had TB or to have been given a TB diagnosis, according to another study [2].

Mycobacterium tuberculosis may infect one-third of the world's population, yet not all infections result in active TB because the immune system usually eliminates the organism. Nonetheless, some individuals may continue to harbor dormant microorganisms. They can become active and lead to disease when paired with risk factors such advanced age, diabetes, and other immunosuppressive medications. After controlling for confounding variables, uncontrolled diabetes mellitus and five additional risk factors were shown to be associated with TB treatment failure. More than five times as many respondents were at risk of not responding to treatment if their diabetes was uncontrolled and their HbA1c level was less than 7% after two months of treatment [6].

An increased risk of recurrence was found to be significantly correlated with uncontrolled DM (HbA1c), according to a systematic study. Similar results from a different multicenter research were obtained in South Korea. As a result, it's critical to carefully evaluate the clinical circumstances and blood glucose levels of TB patients with DM while they're undergoing treatment. A larger risk of worsening TB treatment outcomes was seen in respondents under the age of 45 [7]. Studies carried out in Indonesia have found a similar outcome. Similar to this, poor financial circumstances were also linked to treatment failure.

A study carried out in Kuala Lumpur, Malaysia, however, found no appreciable differences in the economic circumstances of the two groups. Although the majority of research conducted outside of the Middle East did not find a connection between DM and conversion at the end of two months, we took into account a longer observation period of six months [6]. This study aims to identify the relationship between glycemic control and the length of treatment in patients with tuberculosis and diabetes mellitus.

2. Materials And Method

This type of research is analytical observational research with a cross-sectional design. This study aims to determine the relationship between Hba1c laboratory results and the length of recovery in pulmonary TB patients with DM and the effectiveness of intensive phase treatment progress at the Tugurejo Regional General Hospital and Roemani Muhammadiyah Hospital Semarang. This study used a saturated sampling technique or total sampling, namely where all members of the population were sampled, a total of 31 TB patients with DM from December 2019 to August 2023 who met the inclusion criteria.

Inclusion criteria consisted of: early phase pulmonary TB patients, all TB-DM patients, patients aged ≥ 18 years, and willing to be respondents in the study. Meanwhile, the exclusion criteria in this study were TB patients who dropped out of treatment, patients who died and MDR patients. The tools used in this research are medical record data and blood lab results (HbA1c). The data analysis techniques used in this research are univariate and bivariate. Univariate analysis is presented in table form in the form of frequencies and percentages. Bivariate analysis was carried out using the chi square test with significance $\alpha = 0.05$. The research results are said to be meaningful if the results are $p = 0.05$, meaning there is a relationship between the independent variable and the dependent variable.

The ethical aspects of this research are respect for persons by maintaining the confidentiality of subjects and medical records, beneficence and non-maleficence, namely that the research is beneficial and does not harm the patient and finally justice, namely treating patient medical records fairly. This research was conducted after optaining approval from Tugurejo Regional General Hospital Ethics Commission with the issuance of entical approval No.090/KEPK.EC/X/2022.

3. Result

This research was carried out from November 2022 to August 2023 at Tugurejo Hospital, Province. Central Java, Semarang and Roemani Muhammadiyah Hospital, Semarang.

Table 1. The Tuberculosis (TB) with Diabetes Mellitus (DM) patient characteristics

Characteristics	N	Percentage (%)	Mean ±SD	Min	Max
Gender					
Male	17	54,8	-	-	-
Female	14	45,2			
Aged					
≤50 years	9	29,0	53.5±10.8	18	69
>50 years	22	71,0			
HbA1c level					
<7%	5	16,13	7.34±2.53	4.4	14.9
≥7%	26	83,87			
Length of treatment					
≤6 month	18	58,06	-	-	-
>6 month	13	41,94			

Based on Table 1, it was found that the majority of TB-DM patient was male as 17 samples (54.8%), most of the sample aged were > 50 years old as many as 22 samples (71.0%), 26 samples had HbA1c levels ≥7% and majority TB treatment duration ≤6 months were 18 samples (58.06%).

Table 2. Correlation between glycemic control and length of treatment in (TB) with Diabetes Mellitus (DM) Patients.

HbA1c Level	Length of treatment		P-value
	≤6 month N (%)	>6 month N (%)	
<7%	1 (20,0%)	4 (80,0%)	0.083
≥7%	17 (65,4%)	9 (34,6%)	

Based on table 2, the results of the chi-square test show p value = 0.083 p (>0.05), meaning that there is no significant relationship between glycemic control and the length of treatment for TB-DM patients.

4. Discussion

Male predominance among DM pulmonary TB patients has been revealed by this investigation. A widely acknowledged rationale for the greater prevalence of TB among men is that they engage in more social activities than women, which puts them at a higher risk of M. tuberculosis transmission. But this idea is unable to account for the outcomes among DM patients [1]. The prevalence of TB in Indonesia is greater than in men. Fewer female TB cases are associated with smoking habits [8]. The greater number of men who experience pulmonary TB is due to the dominant male smoking habit which causes a decrease in the defence mechanism of the respiratory tract because inhaled cigarette smoke contains toxins so that the respiratory tract is more susceptible to infection. Toxins in cigarette smoke cause damage to phagocyte cells in the respiratory tract and a decrease in response to antigens, as a result of which they are more susceptible to invasion by microorganisms, including Mycobacterium TB which causes pulmonary TB [9].

According to research by O'Leary et al. carried out in Dublin, Ireland, it was discovered that the smokers group's lung compartment had an increase in the number of alveolar macrophages, which indicated a decline in specific immunity and would decrease the immune response to Mycobacterium tuberculosis (MTB) infection. According to one notion, smoking can alter the structural components of Mycobacterium tuberculosis (MTB) exposure. Both healthy individuals and those with tuberculosis will have an increase in their ability to produce lung fluid. Smoking also alters acquired and innate cell immunity, which can have an impact on leukocytes and macrophages [10].

Most TB-DM patients were over 50 years of age. Age was the most prevalent risk factor for the development of TB in DM patients. Latent TB infection (LTBI) is more common in people over the age of 50 than in people under 50 (OR 2.974, 1.149-7.698, p = 0.025). Effective glycemic control has been questioned in relation to its impact on LTBI incidence and immunity. IFN production was demonstrated in one investigation to be reduced in high-glucose conditions [1]. One of the biggest risk factors for contracting TB is just getting

older. Intrinsic processes that promote cell regeneration, repair, and immunosurveillance are weakened by age-related baseline inflammation and an oxidative state, which is known as "inflammaging" [11]. It is challenging to fully comprehend how to prevent or repair inflammatory reactivity and the detrimental effects of aging because it is a very dynamic and intricate process. The scenario is further compounded by the inclusion of all the age-related comorbidities that are currently driving the global tuberculosis epidemic, such as diabetes mellitus (DM), malnutrition, obesity, and HIV. [3].

According to our study, the majority of samples had HbA1c levels under 7%. Patients with TB and DM exhibited a considerably higher prevalence of deteriorating TB treatment than patients with TB alone. Age, inadequate socioeconomic situation, poor glycemic control, and a history of tuberculosis were all significant predictors of worsened treatment outcomes for tuberculosis. Over five times as many respondents were at risk of not responding to treatment if they had uncontrolled DM and a HbA1c level of less than 7% after two months of treatment [6]. Patients with DM and TB have shown that worsening glycemic control necessitates the use of insulin and that there are pharmacological interactions between antitubercular therapy (ATT) and oral antidiabetic medications. Patients with TB and DM have been found to have an insulin resistance state and decreased insulin production as a result of the release of inflammatory cytokines including IL-6 and tumor necrosis factor-alpha [12].

According to the findings, there is no connection between glycemic control and the time spent receiving treatment for TB-DM patients. One year following the start of TB treatment, stable/increasing HbA1c was linked to a pro-inflammatory state characterized by increased plasma cytokines, Th1 (CX3CR1+), and Th17 CD4+ T cell responses [13]. During the first three months of anti-TB medication, there were changes in HbA1c, but these changes were unrelated to variations in the results of TB treatment [14-15]. Although our study did not show worse outcomes in patients with DM and TB, the point that needs to be highlighted is the low rate of follow-up in patients with TB. This probably leads patients to stop therapy and can worsen the existing disease itself and also contribute to the burden of multidrug drug resistant TB.

The limitation of this research is our sample size was small. TB-DM patients who have laboratory data on HbA1c levels are only TB-DM patients who use insulin therapy. There was no data HbA1c levels of TB-DM patients who use oral hypoglycemic agents (OHAs) therapy. Data HbA1c levels obtained were only before initial phase of treatment, there was no data on HbA1c levels after completing the 6 month intensive phase of treatment. A cohort approach would be preferable for future researchers so that HbA1c levels of both TB-DM patients who utilize insulin therapy and OHAs may be compared.

5. Conclusion

The majority of TB-DM patient was male, aged were >50 years old, HbA1c levels >7% and TB treatment duration ≤ 6 months. Glycemic control and treatment duration for TB-DM patients do not significantly correlate.

Authors' Contributions. All authors contributed equally to this work.

Acknowledgments. The authors would like to thanks to the Muhammadiyah University Research and Community Service Institute (LPPM) in financing and regulating the research grants of the Primary Lecturer Research Scheme in 2022.

References

1. A. Chang, C.Z. Wu, J.D. Lin, et al., Prevalence and risk factors for latent tuberculosis among diabetes patients in Taiwan: A cross-sectional study, J Infect Dev Ctries, 2022, vol. 16(4), p.644-649. doi:10.3855/jidc.15839
2. W. Jiang, Trimawartinah, F.M. Rahman, et al., The co-management of tuberculosis-diabetes co-morbidities in Indonesia under the National Tuberculosis Control Program: results from a cross-sectional study from 2017 to 2019, BMC Public Health, 2022, vol. 22(1). doi:10.1186/s12889-022-13017-y
3. World Health Organization, Global Tuberculosis Report 2020, World Health Organization, 2020.
4. International Diabetes Federation. IFD Diabetes Atlas Ninth Edition 2019, 2019
5. C. Ugarte-Gil, B. Alisjahbana, K. Ronacher, et al., Diabetes mellitus among pulmonary tuberculosis patients from 4 tuberculosis-endemic countries: The tandem study, Clinical Infectious Diseases, 2020, vol. 70(5), p.780-788. doi:10.1093/cid/ciz284
6. R.K. Mahato, W. Laohasiriwong, R. Koju, The role of Diabetes mellitus comorbidity on Tuberculosis treatment outcomes in Nepal: A prospective cohort study, South East Eur J Public Health. 2022, vol. 2022 (Special issue 2), p.1-13 doi:10.11576/seejph-5329
7. B. Alisjahbana, E. Sahiratmadja, EJ. Nelwan, et al., The effect of type 2 diabetes mellitus on the presentation and treatment response of pulmonary tuberculosis, Clinical Infectious Diseases, 2007, vol. 45(4), p.428-435. doi:10.1086/519841
8. F.H. Surbakti, S.N. Widada, F. Hikmah, Risk of Elevated Blood Glucose Levels in Tuberculosis Patients with BTA 3+ Levels, Puskesmas Bojong Gede Kabupaten Bogor, Jurnal Analis Medika Biosains (JAMBS), 2020, vol.7(2), p.101-106.

9. R.C. Koesoemadinata, P.F. Hadisoemarto, M.I. Gumilang, I.P. Santoso, B. Alisjahbana, Contribution of Smoking to Pulmonary Tuberculosis Incidence in Bandung, Indonesia, Journal of Epidemiology and Public Health, 2020, p.451-457. doi:10.26911/jepublichealth.2020.05.04.07
10. A. Hasanuddin, J. Syarif, D.E. Artha, Identification of Mycobacterium Tuberculosis in Active Smokers with Ziehl–Neelsen Staining Method, International Journal of Public Health Excellence (IJPHE), 2022, vol. 2(1), p.266-272. doi:10.55299/ijphe.v2i1.204
11. A.M. Olmo-Fontánez, J. Turner, Tuberculosis in an Aging World, Pathogens, 2022, vol. 11(10), p.1-13 doi:10.3390/pathogens11101101
12. J.T. George, A.T. Miraclin, S. Sathyendra, J.S. Michael, J. Prasad, G. Rebekah, Pulmonary tuberculosis and diabetes mellitus: Clinical profile and outcomes, Int J Mycobacteriol, 2022, vol. 11(4), p.400-406. doi:10.4103/ijmy.ijmy_154_22
13. R. Krause, C.M. Warren, J.D. Simmons, et al., Failure to decrease HbA1c levels following TB treatment is associated with elevated Th1/Th17 CD4+ responses, Front Immunol, 2023, vol. 14, p.1-12 doi:10.3389/fimmu.2023.1151528
14. P. Tabarsi, P. Baghaei, M. Marjani, W.M. Vollmer, M.R. Masjedi, A.D. Harries, Changes in glycosylated haemoglobin and treatment outcomes in patients with tuberculosis in Iran: A cohort study, J Diabetes Metab Disord, 2014, vol. 13(1), p.1-6 doi:10.1186/s40200-014-0123-0
15. A. Desai, N. Gupta, L. Korishetty, K. Saravu, Treatment outcomes of patients with tuberculosis and diabetes: A prospective cohort study from India, Int J Mycobacteriol, 2021 Apr-Jun, vol. 10(2), p.111-115. doi: 10.4103/2212-5531.307069. PMID: 34558460.