JKKI: Jurnal Kedokteran dan Kesehatan Indonesia
Indonesian Journal of Medicine and Health
Journal homepage: https://journal.uii.ac.id/JKKI
P-ISSN 2085-4145 | E-ISSN 2527-2950

Type 2 diabetes mellitus as an independent risk factor of pulmonary tuberculosis: A hospital based cross-sectional study

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Original Article

ARTICLE INFO

Keywords:
pulmonary tuberculosis,
diabetes mellitus,
glycated hemoglobin (HbA1c)

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DOI: 10.20885/JKKI.Vol15.Iss2.art9

History:
Received: December 30, 2023
Accepted: August 23, 2024
Online: August 27, 2024

ABSTRACT

Background: The growing frequency of infectious and non-communicable illnesses on a global scale is primarily associated with the changing patterns observed in epidemiology. Diabetes mellitus (DM) significantly leads to the development of tuberculosis (TB) and less effective treatment outcomes if not identified early.
Objective: This study aims to investigate type 2 DM as a risk factor for TB infection.
Methods: Participants in this cross-sectional research study comprised DM patients who reported cough complaints at the TB treatment center and the internal medicine department of Zainoel Abidin Hospital. Random blood glucose and glycated hemoglobin (HbA1c) levels were measured in all respondents. The Chi-Square test assesses the association between DM and Pulmonary TB.
Results: There are 48 DM patients with new pulmonary TB, an averageage of 53 years (SD 9.1). Most of them have symptoms of cough for more than 2 weeks (85.4%), loss of body weight (77.1%), chest pain (58.3%), and loss of appetite (72.9%). The high HbA1c levels were associated with TB, as detected by Xpert MTB/RIF assay and typical radiographic signs ($p<0.05$). DM patients with increased HbA1c were found to have a two times chance of showing results from a chest x-ray typical of TB and probability of TB infection (PR: 2.850, 95% CI (1.152-7.053); 2.745, 95% CI (0.969-7.780)) respectively.
Conclusion: DM patients had two times the risk of lung damage based on chest X-rays and having TB. DM may seriously compromise the efficacy of TB control programs and impede a nation's progress toward TB elimination.

INTRODUCTION

According to the World Health Organization (WHO), DM is a global epidemic which has been observed to predominantly affect both low and middle-class income countries, with 80% of all DM-related deaths occurring in these regions.[1] Additionally, it is essential to acknowledge that regardless of the progress made in addressing TB, this illness continues to rank as one of the top causes of death worldwide.[2] This finding evidenced by the survey results obtained from the WHO, where it was stated that with an estimated 351,936 cases in 2020, Indonesia is one of the nations that contributes to the majority of all TB

infections worldwide.[3]

As stated in previous investigations, 80% of the global loading of DM is concentrated in modest to moderate income countries such as India, China, Brazil, Indonesia, Pakistan, and the Russian Federation. Among these countries, Indonesia ranked as the fifth, calculated for approximately 19.47 million DM patients, resulting in a diabetes prevalence of 10.6% in the country.[4] Furthermore, by considering the significant and adverse impact of DM on the immune system, it becomes clear that DM substantially influences the natural course of TB infection.[5]

Diabetes mellitus has been shown to increase the risk of TB, and it can increase by 2-3 times. Individuals who have both DM and TB are more likely to die while receiving therapy and to relapse when it is over. Diabetes complicated when infectious diseases like TB are present. It has also been demonstrated that managing glucose levels enhances the effectiveness of TB treatment.[6] In this regard, multiple meta-analysis reviews have suggested that individuals with both DM and TB tend to experience less effective therapeutic results when as opposed to those who don't have DM. This is mainly attributed to the challenges faced by patients, which include the non-conversion of sputum after TB treatment, an elevated risk of drug resistance, treatment failure, mortality, and even relapse after the treatment. Furthermore, it has been noted that individuals with TB are more susceptible to hyperglycemia or insufficient glycemic control.[7]

The high epidemiological impact of TB on people with DM is a crucial element in the TB environment. Individuals in this community also face limited access to services, criminalization, and marginalization. Individuals who have DM are susceptible to TB infection and disease, underprivileged, or both. This important group might not be able to obtain health care and other support services due to various social, economic, cultural, and other challenges, including geographic constraints within the Indonesian archipelago. As a result, they might not get the most out of targeted TB screening. Active case finding (ACF) activities were initiated by Indonesia's National Tuberculosis Control Program in 2020. These activities were part of several pilot projects that involved a variety of targeted groups, including detention centers, Islamic boarding schools, farmers, fishing communities, workers in coffee factories, and high-risk groups like those with DM, Human Immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS), and contacts with TB patients. Symptom screening, Chest X-Ray (CXR), if available, and the collection of sputum samples for diagnostic testing utilizing fast molecular TB techniques, as advised via the WHO, are among the primary initiatives of ACF.[8]

In this study, a thorough examination of four trials that considered age and other possible confounding factors was conducted. According to the findings, DM has a five-fold increased risk of dying when receiving TB therapy. Per the results, a population-based study was conducted in Asia and it was found that nearly 20% of the population diagnosed with both TB and DM showed an increased risk of death compared to those with TB alone. Furthermore, patients with these two diseases have been examined to often present changes in the pattern and distribution of atypical lesions, particularly in the lower lung lobes. This finding stands in contrast to TB patients, who typically manifest lesions in the upper lobes, potentially leading to misdiagnoses such as pneumonia or even a tumor. The WHO has shown consistent commitment to 80 % reduction in cases of TB and 90 % reduction in TB-related mortality by 2030. However, DM significantly affects the ordinary course of TB infection, challenging this intervention and control efforts worldwide.9 Based on this understanding, it becomes crucial to collect hospital-based evidence showing the mutual influence of these two diseases. This step is important as it plays a significant role in controlling and curbing The community-wide spread of infection. Therefore, this study aims to assess type 2 DM as a risk factor for TB infection.

METHOD

Study design

This cross-sectional study was carried out at the Endocrine and Directly Observed Therapys (DOTS) Polyclinics of Dr. Zainoel Abidin General Hospital in Banda Aceh. The investigation started in January to July 2023.

Population and sample

Throughout the study period, a total sampling method was employed. Diabetic individuals in

the outpatient unit and over 16 years old were included in the research unit. The age of 17 was selected according to the age distribution of individuals with pulmonary TB to differentiate it from pulmonary TB in children. There was not a maximum age requirement for this study. This study did not include patients who were pregnant, patients who had trouble understanding, or patients who had trouble on moving around because they needed to be transported to the closest hospital for additional testing. The study's sample size used a total sampling technique for 6 months of research. Patients who met the study inclusion requirements and attended the clinic during the study period were sequentially recruited into the study using a method of sequential sampling following the receipt of signed informed consent. In addition, the respondents provided informed consent, and those observed with a persistent cough lasting more than two weeks were included after an extensive clinical assessment.

Data collection

Initial screening begins with the selection of an assortment of patients who report a cough lasting more than one week, weight loss, fever (especially in the afternoon), decreased appetite, and body fatigue using CXR examination. Additionally, CXR was performed in the posterior/anterior view. It is important to comprehend that patients diagnosed with Type 2 DM who had a sequelae of TB and the present research did not include participants with extra-pulmonary TB. Sputum testing with Xpert Mycobacterium Tuberculosis-Rifampicin (MTB/RIF) is one of the molecular testing methods for TB, samples from every individual's morning phlegm were taken and delivered to the microbiology laboratory for rapid molecular testing using Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA, United States) and clinical assessment based on objective criteria.

Since this study was conducted in an internal medicine unit and a TB service unit, there were several concerns in selecting subjects for the study. Diabetes mellitus participants who were receiving treatment for TB at the time of recruitment and who had received a TB diagnosis before the trial were included as research units DM patients who, at the time of symptom assessment, had an active cough lasting more than two weeks were referred for CXR and submitted a sputum sample to the laboratory for Xpert MTB/RIF molecular testing to detect Mycobacterium TB. A positive Xpert MTB/RIF result confirmed the bacteriological diagnosis of pulmonary TB and anti-TB drug therapy. Individual DM who had x-rays with typical TB features underwent further clinical evaluation and monitoring by a pulmonary specialist to determine the diagnosis of clinical pulmonary TB.

Additionally, specimens of blood were taken in order to assess the blood glucose randomly and glycated hemoglobin (HbA1c) levels. The results of the typical TB CXR include cavities, infiltrates, fibro infiltrates, fibrotic, miliary patterns, consolidations, and pleural effusion.[10]

Data analysis

The present study applies descriptive analysis to explain characteristics, clinical symptoms, and blood glucose levels of patients. The categorical data was then analyzed using the chi-square test at a significance threshold of less than 0.05. The statistical procedures used in this investigation were performed using SPSS Edition 21.

Ethics

This research received approval from the research ethics committee of Dr. Zainoel Abidin General Hospital, Banda Aceh (Ethics Committee Number: 005/ETIK-RSUDZA/2023).

RESULT

Data has been collected from 48 patients with DM and pulmonary TB for this investigation. The majority of respondents were males (68.8%), with an average age of 53.89 years and a standard deviation of 9.1 years. Furthermore, approximately two-thirds of the examined individuals had positive TB test results for Mycobacterium tuberculosis (MTB) in the sputum. The most frequently observed clinical symptoms among these individuals was a cough lasting more than two weeks, followed by night sweats, weight loss, decreased appetite, and chest discomfort. It is also crucial to state that among the DM patients with pulmonary TB, a significant proportion (62.5.4%) had MTB detected by Xpert MTB/RIF Assay sputum test results, with 48 out of 62.5% being positive. Additionally, 18 (37.5%) patients were found to have negative Xpert MTB/RIF assay

test results. In this study, it is also found that the upper lobes are the most common location for typical TB lesions, calculating for 58.3% of cases (Table 1).

The blood glucose examinations carried out in this investigation shows an average HbA1C of 11.7% within the range of 5.3-15.0. Since the data is not normally distributed, the categorization of

Table 1. Common characteristics of DM individuals with lung TB

Characteristics	Description	Frequency/percentage (n/%)
Gender	Male	33 (68.8)
	Female	15 (31.3)
Occupation	Housewife	7 (14.6)
	Self-employed	11 (22.9)
	Civil servant	3 (6.3)
	Farmer	1 (2.1)
	Retiree	5 (10.4)
History of previous TB	Yes	8 (16.7)
	No	40 (83.3)
Glycated Hemoglobin (HbA1C) level	High	23 (47.9)
	Low	25 (52.1)
Xpert MTB/RIF assay	*Mycobacterium tuberculosis* detected	30 (62.5)
	Mycobacterium tuberculosis not detected	18 (37.5)
TB's CXR appearance	Typical TB	34 (70.8)
	Atypical TB	14 (29.2)
Clinical complaints characteristics		
Coughed for longer than two weeks.	Yes	41 (85.4)
	No	23 (14.6)
Intermittent fever	Yes	19 (39.6)
	No	29 (60.4)
Night sweats	Yes	19 (39.6)
	No	29 (60.4)
Weight loss	Yes	37 (77.1)
	No	11 (22.9)
Chest Discomfort	Yes	28 (58.3)
	No	20 (41.7)
Loss of appetite	Yes	35 (72.9)
	No	13 (27.1)
Location of TB lesions	Superior Lobe	28 (58.3)
	Medius Lobe	2 (4.2)
	Inferior Lobe	18 (37.5)

DM: diabetes mellitus; HbA1C: Glycated hemoglobin; Xpert MTB/RIF: Xpert *Mycobacterium tuberculosis*-Rifampicin; CXR: Chest X-Ray

HbA1c levels uses the median value. HbA1C levels are categorized as "low" if the result is below 11.7% and "high" if it is above 11.7%. Similarly, random blood glucose levels shows an increase with median of 250.50 mg/dl (10-516) (Table 2).

This study identifies a correlation between HbA1c levels and the positivity of MTB based on sputum examination. This examination was conducted using a molecular fast test and the CXR results indicating typical TB ($p<0.05$). Based on this exploration, it is shown that every patient had a two times greater likelihood of a CXR displaying typical TB characteristics and two times increased risk of MTB infection (Table 3).

Table 2. Blood glucose level

Blood glucose level	Median (Minimum-Maximum)
Random blood glucose	250.50 gr/dl (10-516)
Glycated hemoglobin (HbA1C) level	11.7 % (5.3-15.0)

Table 3. Correlation between glycated hemoglobin (HbA1C) level, molecular sputum test, and CXR

Variables	HbA1C		Total	PR	p-value
	High	Low			
Mycobacterium tuberculosis detected	19	11	30	2.850 (1.152-7.053)	0.01*
Mycobacterium tuberculosis not detected	4	14	28		
CXR Typical Tuberculosis	20	14	34	2.745 (0.969-7.780)	0.04*
CXR Atypical Tuberculosis	3	11	14		

HbA1C: Glycated hemoglobin; CXR: Chest x Ray: PR: Prevalence Ratio; *chi-square analysis, significancy p value < 0.05

DISCUSSION

This study shows the risk of tuberculosis is almost three times higher in those with poor glycemic control. In the latest study, glycemic control was assessed using HbA1c, and proposed that individuals with more severe diabetes have a higher risk of getting tuberculosis. Chronic hyperglycemia in diabetic individuals increases the risk of hypoxia, which elevates venous system pressure and promotes MTB growth. Insulin therapy significantly improv the weakened host defense against MTB infection in diabetics, which was found to be caused by lower production of Th1-related cytokines and NO in a mouse model.11 This study highlights that people with TB are two times more likely to contract TB and five times more likely to have typical TB CXR results. Additionally, "atypical" CXR abnormalities, such as lower lobe lesions, are more common in DM-TB patients, especially in people with inadequate glucose regulation.12 The occurrence of typical TB in the current study, such as fibro infiltrate, cavities, and patients with hyperglycemia, were more likely to have more involvement in the upper lobe of the lungs.

This study shows that the HbA1C level of DM patients was 11.7% and is categorized as "low" if below 11.7% and "high" if above 11.7%. Similarly, random blood glucose levels shows an increase, with a median value of 250.50 mg/dl. As indicated in the previous study that TB may impair insulin sensitivity through a number of different pathways. Those who have diabetes, however, may also be more susceptible to infection because of increased MTB exposure. This may develop because persons with diabetes have altered immune systems, which increases the likelihood of an initial infection, or because they utilize healthcare facilities more frequently. A recent comprehensive investigation showed that people with diabetes has a slightly greater risk of contracting MTB contamination (RR 1.18, 95% CI 1.06 to 1.30).[13] One of these mechanisms is inducing the production of stress chemicals like cortisol, which elevate blood glucose levels. Additionally, pancreas activity may be hampered by the secretion of more chemokines and cytokines and the buildup of TB proteins in the organ, leading to reduced insulin production and resulting in glucotoxicity.[14]

Hyperglycemic individuals are more likely to develop cavitary lung lesions, have unfavorable treatment results, and die after therapy. The

CXR revealed that lung cavities and parenchymal abnormalities are more common in diabetes patients. Patients with diabetes who do not control their blood sugar levels are more likely to have abnormal results from thoracic CT and CXR, including more cavities ($p<0.001$), advance severe lesions ($p<0.001$), and involvement of all lobes. It has been proposed that hyperglycemia in DM patients increases the incidence of lobe lesions and the formation of lung cavities in TB-DM patients, exacerbating TB pathogenesis. Persistent kidney disease and hemodialysis raise the likelihood of developing tuberculosis by 6.9 to 52.[5] fold as opposed to the overall population. A further danger sign for the spread of TB infection is persistent kidney failure. Therefore, the second type and primary diabetes both lower the body's defenses to tuberculosis, which raises the risk of system pathological conditions, vulnerability to disease, anti-TB therapy problems, and tuberculosis-related mortality.[15]

According to earlier research, hyperglycemia worsened pulmonary radiographic presentation in TB patients and raised the probability of pulmonary tuberculosis incidence.[16] Compared to patients with normoglycemia, hyperglycemia-related TB patients were more likely to have cavities and alveolar infiltrates. Similarly, the results of this study demonstrate that most hyperglycemic individuals have a CXR that is characteristic of tuberculosis. On chest Computed Tomography (CT), Individuals with poorly controlled diabetes are prone to have greater lobe involvement if their HbA1c is more significant than 9% and more cavities in the lower lung area. Higher levels of the cytokines Interleukin 17-A (IL-17A), Interleukin 8 (IL-8), and Interleukin 10 (IL-10) are produced in the lung by hyperglycemia and oxidative stress, which worsens the pro-inflammatory response. Patients with DM have severely diminishes functions of neutrophils, macrophages, Dendritic cell (DC), and Natural Killer (NK) cells, among other innate immune components. This results in delayed antigen presentation and decreased microbicidal activity. Patients with diabetes who are receiving anti-TB medication have shown signs of persistent inflammation.[12] It has been suggested that increased cytokine production, including C-Reactive Protein (CRP), was linked to increased neutrophil recruitment and infiltration in TB-DM patients. This, in turn, caused increased inflammation and necrosis, which may have eventually contributed to cavity development.[17]

Individuals with diabetes have a multifactorial and many mechanisms higher risk of tuberculosis . Diabetes is a chronic illness that weakens the immune system, making it harder for the host to fight infections. Diabetes has been linked to cytokine production impairment, leukocyte recruitment inhibition, and immune cell dysfunction, including neutrophil, macrophage, and natural killer cell dysfunction. Apart from impeding cellular immunity, it may also impact the complement effector system and the generation of antibodies. Cellular immunity is diminished as a result of decreased T-cell quantity and activity as well as a low neutrophil count. When compared to their non-diabetic counterparts, diabetics have lower levels of T helper 1 (Th1), tumor necrosis factor-α (TNF-α), Interleukin 1(IL-1), and Interleukin 6 (IL-6). Diabetic individuals are more vulnerable to tuberculosis because of diminished T-cell generation and activity, specifically the suppression of Th1 cytokines from Mycobacterium tuberculosis. Diabetes causes macrophage dysfunction that impairs phagocytic, chemotactic, and reactive oxygen species production. Individuals with diabetes also have impaired monocyte chemotaxis, a condition that is unaffected by insulin. It is also believed that hyperglycemia weakens the respiratory burst's ability to drive out bacteria. Even if these suggested mechanisms make sense, it's crucial to conduct additional research to determine whether or not they are accurate. Blood glucose problems may also be related to the oxidative stress response to infection, which is mediated by the actions of TNF-α, IL-1, and IL-6.[18]

The high incidence of type 2 diabetes puts at risk the progress gained in lowering the global burden of tuberculosis. Due to its tendency to raise the risk of tuberculosis, TB poses a severe hazard to the public, especially in nations where both diseases are common. Experts expressed far greater alarm over the DM and TB epidemics combining.[19] In this study, a greater proportion of males made up 68.8% of patients with both DM and pulmonary TB, compared to females (31.3%). The observation is in line with the results of an investigation conducted in Sri Lanka, which screened infected patients and signified the highest prevalence of TB in males having DM with poor

glycemic control. Therefore, male patients having poor glycemic control in this context appear to be more prone to the risk of TB. Other studies have also showed that women tend to have 20-30% lower TB rates after the age of 40.[20] This study also discovers that for men, but not for women, DM is substantially associated with an increased risk of recurrent tuberculosis after stratifying the data by sex. We are unable to fully determine the reason behind the variance in the effect of DM on TB recurrence depending on gender in our investigation. Additional factors, like smoking, drinking, and Chronic Obstructive Pulmonary Disease (COPD), may be complicating factors. On the other hand, we ignore these factors.[21] Consequently, confounding factors can be counted for a gender-related difference in the effect of DM on TB relapse.

The most prevalent TB symptoms among the examined individuals in this investigation included cough, decreased appetite, and dropping weight. This finding is in line with results from prior studies However, some reports showed that the presence of DM could potentially lead to a more severe form of the disease.[22] The most prevalent sign of respiratory illnesses, such as tuberculosis, is cough, and 20% of TB patients also experience hemoptysis.[13] While this study shows that cough for more than 2 weeks (85.4%), loss of body weight (77.1%), chest discomfort (58.3%), and loss of appetite (72.9%). Chest discomfort is a crucial finding from this study since it represents clinical manifestations that have not been frequently observed in several other studies before. According to a study, DM patients' cough remained the most common sign of pulmonary TB. Usually, hemoptysis affects 20% of patients. Hemostasis occurred more frequently in men.[23] Hemoptysis has not been detected in any DM patients with TB, according to another investigation. Contrary to what the study's findings indicated, chest pain is the most common complaint among DM patients with TB at our hospital, and hemoptysis is not identified in this study as a clinical symptoms of tuberculosis. A fever is a common indicator of an infectious illness. It may be absent in 29% of TB patients, mainly in older patients or people with diabetes.[24] Nearly 60% of our DM patients have not experienced feverish responses.[22]

The result leads to the conclusion that DM escalated the impact of TB. While the complete pathophysiology of both diseases remains unclear, changes in the immune system have been described in patients with active TB and DM. These changes include decrease activation of alveolar macrophages, reduce production capacity of interleukin 10, alterations in Th1 cytokines, and adjustments in the innate response. As a result, DM patients are more susceptible to infections caused by the same bacteria, indicating an increased vulnerability to TB.[25]

In a recent exploration, Gautam et al. conducted An observational investigation meta-analysis in 2020. This investigation indicated DM was extremely common in TB patients, particularly in South Asia, and was established that individuals with DM suffering from TB are more likely to experience adverse outcomes, such as a greater probability of death and treatment failure, although this association was not linked to multi-drug-resistant TB.[26] Previous studies also emphasized the importance of accentuating the necessity of screening the hyperglycemia state and attaining optimal glucose control in those suffering from tuberculosis to improve outcomes from therapy.[27] Given the prevalence of DM as a prevalent non-communicable illness, it is essential to conduct a comprehensive investigation of the relationship with the level of glucose tolerance disturbances possessed by TB patients.

Our study has limitations. Since pulmonary tuberculosis (TB) has become a widespread infection among the upper socioeconomic group, this study was carried out at a tuberculosis service facility in Banda Aceh City that serves a group of patients from the province's lower socioeconomic group. Patients with TB who also have long-term co-morbid conditions, such as coronary artery disease and elevated blood pressure, may visit routine health clinics instead of DM clinics. It means some of these patients are left out of the study units, which might be seen as a study constraint.

CONCLUSION

This study shows that DM is at high risk of being infected with TB and has lung TB lesions, as proven by CXR. As a result, it is found that improved knowledge of the reciprocal relationship between these two illnesses was necessary for effective organizing and collaboration to address the double weight. It is recommended

to integrate both diseases' mitigation, screening, and management, as this approach appeared to be more effective. Lastly, recommendations are made, indicating that additional extensive follow-up research be conducted to address issues regarding the scarcity of data on the connection between TB and DM. This study also suggests to emphasize the necessity for cooperation on better screening techniques and when to evaluate MTB sputum in patients with diabetes.

CONFLICT OF INTEREST

There are no competing interests regarding this research.

ACKNOWLEDGEMENTS

We are grateful for the funding provided by Universitas Syiah Kuala for this study's endeavor.

AUTHOR CONTRIBUTIONS

Concept & Research Question: BY, Conducting Research: AD, BY, Statistical Analysis: SF&DS, Report Writing: BY, NA

LIST OF ABBREVIATIONS

ACF: active case finding; COPD: chronic obstructive pulmonary disease; HIV/AIDS): human immunodeficiency virus infection/acquired immune deficiency syndrome; CT: computerized tomography; CXR: chest X-ray; DOTS: directly observed therapys; DM: diabetes mellitus; MTB: Mycobacterium tuberculosis; TB: tuberculosis; WHO: World Health Organization; HbA1C: glycated hemoglobin; Xpert MTB/RIF:Xpert Mycobacterium tuberculosis-Rifampicin; IL-17A: interleukin 17-A; IL-8: interleukin 8; IL-10: interleukin 10; DC: dendritic cell; NK cells: natural killer cells: CRP: C-reactive protein; Th1: T helper 1; TNF-α: tumor necrosis factor; IL-1: interleukin 1; IL-6: interleukin 6.

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