



Type 2 Diabetes Mellitus and Pulmonary Tuberculosis : Literature Review of A Bidirectional Relationship

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ABSTRACT

Background: Type 2 diabetes mellitus is a major health problem worldwide. In spite of the high incidence and prevalence, T2DM is often associated with pulmonary tuberculosis infection which is also a world health burden. T2DM is a chronic condition that suppresses immune system. T2DM increases 3 times the risk of pulmonary TB, increases the risk of pulmonary TB relapse, and causes higher mortality. **Objectives:** In this literature review, writers aimed to provide an overview of the relationship between T2DM and pulmonary TB including epidemiology, risk factor, pathogenesis, clinical manifestation, screening, treatment and prognosis. **Methods:** This literature review is conducted by searching for articles using online search engine, including PubMed and Google Scholar. The selected articles include research articles, systematic reviews, meta-analyses and literature reviews published between 2015-2023 and are limited to those in English or Indonesian which are available in free full text. **Discussion:** T2DM is a risk factor for the occurrence of pulmonary TB. It also increases the severity of disease, incidence of relapse and MDR-TB. On the other hand, pulmonary TB worsening uncontrolled T2DM. Treatment of both T2DM and pulmonary TB must be adjusted if the two diseases co-occur. Mortality of pulmonary TB patients with T2DM is higher than pulmonary TB without T2DM. **Conclusion:** T2DM and pulmonary TB are correlated to each other, having a bidirectional relationship.

Keywords: diabetes mellitus, literature review, literature searching, pulmonary tuberculosis

ABSTRAK

Latar Belakang: Diabetes melitus tipe 2 merupakan masalah kesehatan dunia. Selain kasusnya yang tinggi, DM tipe 2 sering kali dikorelasikan dengan kejadian infeksi tuberkulosis paru yang juga merupakan beban dalam kesehatan dunia. DM tipe 2 adalah penyakit bersifat kronis yang dapat melemahkan sistem kekebalan tubuh. Hal ini dapat meningkatkan risiko terjadinya infeksi TB paru 3 kali lebih besar dibandingkan non-DM, meningkatkan risiko reaktivasi TB paru serta menyebabkan mortalitas yang lebih tinggi. **Tujuan:** Kajian literatur ini bertujuan untuk membahas dan merangkum berbagai literatur terkait hubungan DM tipe 2 dan TB paru yang meliputi epidemiologi, faktor risiko, patogenesis, manifestasi klinis, skrining, pengobatan, dan prognosis, guna meningkatkan pengetahuan mengenai hubungan DM tipe 2 dan TB paru. **Metode:** Kajian literatur ini disusun dengan pencarian literatur dari PubMed dan Google Scholar. Artikel yang dipilih meliputi artikel penelitian, systematic review, meta-analysis, dan kajian literatur. Pencarian artikel terbatas pada publikasi berbahasa Inggris dan Indonesia yang tersedia dalam bentuk free full text dengan tahun publikasi 2015-2023. **Pembahasan:** DM tipe 2 menjadi faktor risiko untuk terjadinya TB paru, meningkatkan keparahan penyakit TB paru, meningkatkan risiko relaps serta kejadian MDR TB. Sebaliknya, TB paru menyebabkan DM tipe 2 menjadi sulit terkontrol. Pengobatan DM tipe 2 dan TB paru harus disesuaikan jika kedua penyakit tersebut terjadi bersamaan. Mortalitas pasien TB paru meningkat pada kondisi DM tipe 2. **Kesimpulan:** DM tipe 2 dan TB paru saling mempengaruhi satu sama lain sehingga memiliki hubungan yang timbal balik.

Kata Kunci: diabetes melitus, kajian literatur, pencarian literatur, tuberkulosis paru

Received [16 Sep 2023] | Revised [30 Sep 2023] | Accepted [30 Sep 2023]

INTRODUCTION

Diabetes Mellitus (DM) is currently a serious global public health problem.^[1] As much as 537 million adults (aged 20 - 79) are diagnosed with DM worldwide and this number is estimated to reach 643 million in 2030 and 783 million in 2045.^[2] Of all DM cases, T2DM has much larger proportion than type 1 DM.^[3] T2DM is diagnosed in 462 million adults worldwide and will continue to increase.^[4] Beside the high incidence, DM is also often associated with the incidence of infectious diseases, one of which is pulmonary tuberculosis (TB).^[5] Pulmonary TB is also a primary health concern worldwide. In 2021, 5.3 million adults globally were suffering from pulmonary TB and it became the 2nd leading cause of infection-related death.^[6] High prevalence of T2DM along with pulmonary TB causes a double burden to global health.^[7] Many things are thought to be related between T2DM and pulmonary TB. T2DM is often considered a risk factor for pulmonary TB.^[8] The role of T2DM in treatment failure of pulmonary TB is also concerning.^[9]

In this literature review, writers aimed to provide an overview of the relationship between T2DM and pulmonary TB including epidemiology, risk factor, pathogenesis, clinical manifestation, screening, treatment and prognosis, in hope this review can be an insight for future research.

METHODS

This literature review was conducted by searching for articles using online search engine, including PubMed and Google Scholar. Keywords used include (Type 2 Diabetes mellitus OR Diabetes mellitus type 2 OR *Diabetes melitus tipe 2*) AND (Pulmonary tuberculosis OR Lung tuberculosis OR *Tuberkulosis paru*). The selected articles include research articles,

systematic reviews, meta-analyses, and literature reviews published between 2015-2023 and are limited to those in English or Indonesian which are available in free full text. Total of 21 articles are included in this literature review.

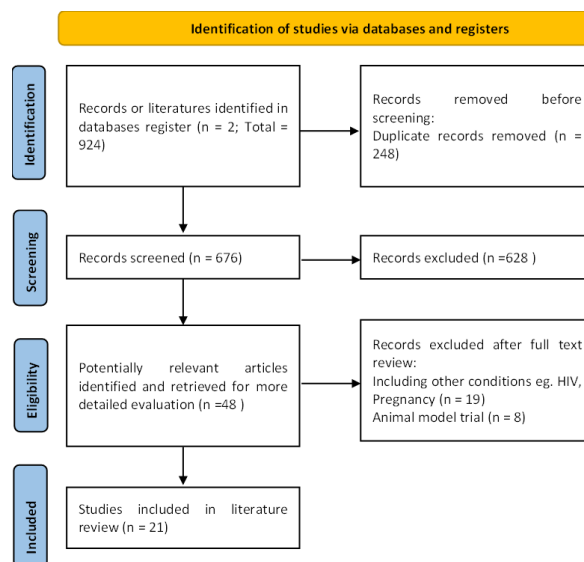


Figure 1. Literature search flow chart

DISCUSSION

Epidemiology of T2DM and Pulmonary TB

Based on a meta-analysis study on the incidence and prevalence of pulmonary TB in T2DM patients which was conducted between 1998-2018, the incidence and prevalence of pulmonary TB in T2DM patients were globally high. From 2.6 million T2DM patients, incidence and prevalence of pulmonary TB were 129.89 per 100,000 (95% confidence interval (CI): 97.55-172.95) and 511.19 per 100,000 (95% CI: 375.94-695.09) consecutively. Incidence and prevalence of pulmonary TB in T2DM patient were significantly higher in countries with higher TB burden. Prevalence of pulmonary TB in T2DM patients was 692.15 per 100,000 (95% CI: 468.75-1022.4) in TB endemic countries, while in nonendemic countries was 105.01 per

100,000 (95% CI: 72.55-151.98).^[10] A high prevalence of T2DM was also found in pulmonary TB patients.^[11]

T2DM as A Risk Factor for Pulmonary TB

T2DM has always been known to be risk factor for pulmonary TB. The relative risk of pulmonary TB in T2DM patients was 3.1 compared to non-DM. This is because of immune response suppression in T2DM patients which makes them susceptible to pulmonary TB infection.^[12] T2DM is also known to aggravate pulmonary TB infection. T2DM increased the risk 5.25 times for the occurrence of large lesion pulmonary TB.^[13] The incidence of Multi Drug Resistant (MDR) TB is often associated with T2DM. This is because pulmonary TB patients who also suffer from T2DM tend to experience treatment failure. From a pharmacokinetic study, plasma level of rifampicin was 53% lower in T2DM patients, this often caused failure in the treatment of pulmonary TB in T2DM patients.^[14] A history of T2DM for >5 years was also a risk factor for pulmonary TB.^[15]

Pathogenesis

In T2DM, there is impaired immune function and decreased immunologic response. A decreased immunological response in a person can facilitate the development of infectious diseases, including pulmonary TB.^[16] Type 2 DM causes delayed immune response in innate immunity and adaptive immunity. From a study, T2DM was known to cause delayed antigen presenting cell (APC) and T-helper cell activation. These immunologic responses are important to inhibit the replication of *M. tuberculosis*. Hence, pulmonary TB infection become more extensive and severe in T2DM patients.^[17]

Clinical Manifestation

Studies showed that T2DM was associated with a more severe clinical course of pulmonary TB including severe cavitation and more extensive lung damage on radiological examination. High HbA1c levels were correlated with larger cavities and large pulmonary TB lesions.^[18] Acid fast bacteria (AFB) smear in pulmonary TB with T2DM tend to have a positive value compared to pulmonary TB without T2DM. In pulmonary TB with T2DM patients, 14 (17.28%) showed AFB positive 3, 15 (18.52%) showed AFB positive 2, 15 (18.52%) showed AFB positive 1 and 37 (45.68%) showed negative (-) AFB. In pulmonary TB without T2DM patients, 3 (2.08%) showed AFB positive 3, 6 (4.17%) showed AFB positive 2, 19 (13.19%) showed AFB positive 1 and 112 (77.78%) showed negative (-) AFB.^[19] Hyperglycemia in T2DM causes delayed sputum conversion. From a study, in pulmonary TB with T2DM patients, AFB smears were still positive after more than 2 months of treatment.^[20] Fasting blood sugar levels in T2DM patients with pulmonary TB tend to be higher than in T2DM patients without pulmonary TB. Fasting blood sugar levels in T2DM patients with pulmonary TB were 1.3 times higher than T2DM patients without pulmonary TB.^[16]

Screening

Screening for T2DM is recommended in new pulmonary TB cases.^[21] Screening is carried out by examining fasting blood sugar levels, post prandial and HbA1c.^[22] The purpose of screening is to increase the success of pulmonary TB therapy.^[23] Screening for pulmonary TB is also recommended for T2DM patients who are in pulmonary TB endemic areas. Screening is carried out using the GeneXpert method and sputum culture.^[24] The aim of screening is to find early cases of active and latent pulmonary TB.^[25]

Treatment and Its Outcome

Treatment for pulmonary TB with T2DM is using the same oral antituberculosis (OAT) regimen as for pulmonary TB without T2DM, but the duration of treatment is extended (>6 months). Patients who receive both OAT and oral antidiabetic are known to have more uncontrolled hyperglycemia than patients with no OAT use. This is because OAT especially rifampicin decreases the plasma concentration of oral antidiabetic so its effectivity is also lowered. Therefore, insulin is recommended for patients with T2DM and pulmonary TB as insulin is not affected by OAT.^[26] Metformin, an oral antidiabetic, is recommended as an adjuvant therapy for pulmonary TB patients. Metformin plays role in better treatment outcome in pulmonary TB as it increases immune response.^[27]

Treatment failure and the incidence of MDR TB are associated with low plasma levels of rifampicin. Decreased intestinal motility in T2DM causes reduced absorption of rifampicin. Therefore, plasma rifampicin levels are low and therapeutic doses are not achieved.^[14] Uncontrolled DM with HbA1c ≥ 7 patients are in greater risk for delayed AFB smear conversion (after more than 2 months of therapy).^{[18][19]}

Successful pulmonary TB therapy is found to be higher in T2DM patients with controlled blood sugar levels.^[28]

Prognosis

All-cause mortality in pulmonary TB patients with T2DM was 14.89% compared to only 12.4% in pulmonary TB patients. T2DM patients with the use of metformin and insulin showed a lower incidence of death.^[29] Pulmonary TB patients with T2DM had a risk of 6.8 times

(95% CI: 2.0-23.7, $p=0.003$) to have MDR TB.^[30] Pulmonary TB patients with T2DM were in greater risk for relapse (OR 2.83, 95% CI 2.60-2.92, $p<0.001$).^[20]

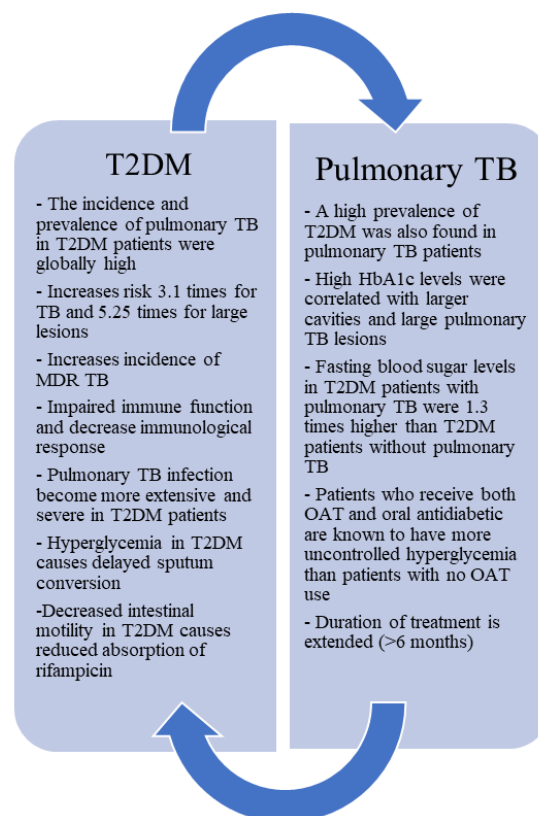


Figure 2. Bidirectional relationship of T2DM and pulmonary TB

CONCLUSION

T2DM and pulmonary TB are both major global public health problems. The frequent occurrence of the two diseases together turns out to be a double burden worldwide. T2DM is a risk factor for the occurrence of pulmonary TB, increases the severity of pulmonary TB disease, increases the risk of relapse and the incidence of MDR TB. On the other hand, pulmonary TB causes uncontrolled T2DM. Screening is recommended for both T2DM and pulmonary TB patients for early diagnosis and optimal therapy. Treatment duration of pulmonary TB in T2DM patients is extended to more than 6 months. Insulin is recommended for

T2DM in pulmonary TB patients. Pulmonary TB therapy failure is associated with low plasma rifampicin levels and uncontrolled blood sugar levels in T2DM patients. Mortality of pulmonary TB patients with T2DM is higher than pulmonary TB without T2DM.

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