

The Relationship between Diabetes Mellitus and Pulmonary Diseases: A Systematic Review

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ABSTRACT

Diabetes mellitus (DM) as a chronic disease could lead to micro- and macrovascular disorder. Also, some evidence demonstrated that pulmonary involvement is more frequent in DM patients than the healthy population. Hence, we tried to perform a systematic search to considering pulmonary disease among the DM patients.

Articles were identified through searching databases including PubMed, Google Scholar, Web of Sciences, Embase and Scopus from 2000 to 2016. We reviewed systematically all studies reporting pulmonary disease among the diabetic patients.

A total of 452 relevant records were identified by the electronic search, of which a total of 19 studies were identified as eligible papers that were original articles for the frequency of pulmonary disease among patients with DM. The incidence of pulmonary diseases has reported among diabetic patients that TB was reported to have a higher frequency when compared to other pulmonary disorder in diabetic patients. Therefore, conducting further studies on these two disorders is recommended, particularly in regions where the incidence of diabetes is increasing rapidly, and tuberculosis remains endemic.

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Introduction

Diabetes mellitus (DM) is a group of chronic and metabolic disorders characterized by hyperglycemia that is a micro and macrovascular disorder. Chronic hyperglycemia is one of the leading problems caused by DM, the most common symptoms of which include frequent urination and increased thirst and hunger (1). Several studies have reported pulmonary

involvement in diabetic patients. Advanced glycation end product is secondary to chronic hyperglycemia in diabetes.

Pulmonary diseases are classified into the inflammatory pulmonary disease, respiratory and lower respiratory tract infections based on organs or tissues involved, type and pattern of the associated symptoms, or their etiology.

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Treatment of pulmonary diseases is of crucial importance as they impose an inordinate burden on health care resources (2).

Despite controlling for potential confounders such as age, height, and smoking status, reduced forced vital capacity (FVC) and forced expiratory volume in the first second (FEV₁) observed among diabetic patients (3). Moreover, according to the Third National Health and Nutrition Examination Survey (NHANES III), FEV₁ is lower in diabetic patients as compared to non-diabetic patients, and an association between glycemic markers and FVC is reported (4).

There is a scarcity of studies on the involved mechanisms of pulmonary function in diabetic patients; however, several studies have reported pulmonary involvement in diabetic patients (5). Hence, we aimed to review the frequency and the type of pulmonary diseases among diabetics patients.

Materials and Methods

Databases and search strategies

We retrieved articles on pulmonary diseases, and DM published during 2000-2016 through surveying databases including PubMed, Google Scholar, Web of Sciences, Embase and Scopus. Search for the related studies was conducted using following keywords: "Lung diseases", "Respiratory diseases" and "Diabetes mellitus."

Inclusion and Exclusion Criteria

Published studies were regarded qualified for analysis if they met the following criteria: (1) Studies with full text of the paper available in English language; (2) Original and clinical studies that assess the frequency and the type of pulmonary diseases among DM patients. Also, Non-English reports, reviews and meta-analysis, case reports, expert opinions, consensus statements, editorials, letters, and qualitative studies were excluded.

Finally, some variables such as sample size, age, gender, type of diagnosis, the rate of comorbidity, controlled intervening variables, and pulmonary diseases related to DM were evaluated in this review article.

Quality Assessment

Quality assessment was independently performed by 2 reviewers using Newcastle-Ottawa quality assessment scale, which consists of 9 questions in 3 sections (selection, comparability, and exposure section). The quality of the studies was evaluated by examining 9 questions and each question had to be answered with "yes", "no", or "unclear". An answer of "yes" got the score of 1, indicating a low risk of bias, whereas an answer of "no" or "unclear" gained a score of "0", suggesting a high risk of bias may exist (6).

As the included studies did not have common outcomes; we did not perform meta-analysis in this study. PRISMA flowchart is shown in figure 1.

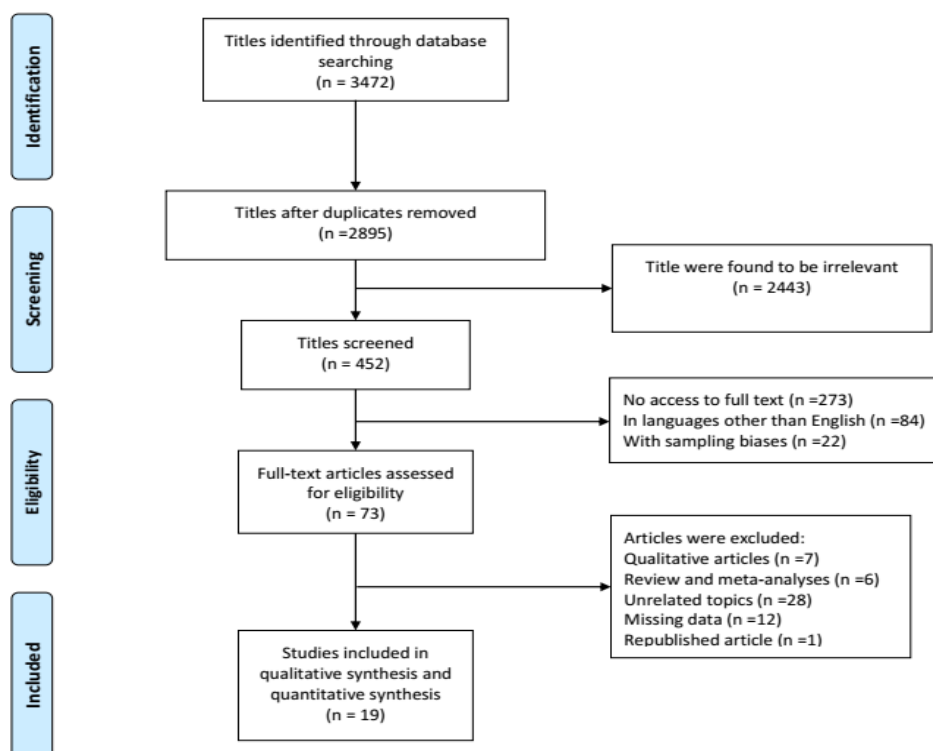


Figure 1. Screening process for the retrieved articles based PRISMA (Preferred Reporting Items for Systematic Reviews And Meta-Analysis)

Results

After retrieving 452 articles, 73 related articles were selected as our final database. Subsequently, seven qualitative articles, six review articles and meta-analyses, 29 articles with unrelated topics, 12 articles with missing data, and one republished article were excluded.

Finally, 19 original articles were entered in this study (Figure 1).

In the present study, some variables including sample size, age, diagnosis criteria, controlled intervening variables, type of pulmonary diseases, and outcome were investigated. Table 1 demonstrates the information regarding the 19

Table 1. Evaluation of some variables associated with pulmonary diseases concomitant with diabetes based on the literature review

Authors/P ublication Year (Reference)	Country	Type of study	Sample size	Age (years)	Diagnosis of DM	Comorbidity	Controlled intervening variables	Pulmonary diseases	Outcome	Study Quality (+to++++)
Mannino et al. (2008) (6)	USA	Cohort study	15341	45-64	DM: post- glucose load glucose levels (>140 mg-dL ⁻¹)		Age, gender, ethnicity, smoking, BMI, and level of education	COPD	Pulmonary dysfunction is associated with a higher risk of comorbidity and mortality	+++
Rana et al. (2004) (7)	USA (Massach usetts)	Cohort study		30-55	---		Age, ethnicity, current weight and height, smoking, physical activity, dietary intake, comorbid conditions	Asthma, COPD, emphysema , or chronic bronchitis	COPD, but not asthma, is a risk factor for developing type 2 DM	+++
Alisjahban a et al. (2007) (8)	Indonesi a	Cohort study	634	≥15	DM: mea surement of FBG concentratio ns	14.8%	Age, gender, and BMI	TB	DM had a negative effect on the outcome of TB treatment. Screening for DM in patients with TB is necessary	++
Dooley et al. (2009) (9)	USA (Marylan d)	Cohort study	297	40-57	DM: oral hypoglycemi c, or had non-fasting glucose measureme nt>200	14%	Age and BMI	TB	DM is a risk factor for mortality in TB patients	+++
Leung (2008) (10)	China	Cohort study	42116	65≤	DM: fasting plasma glucose level>7.0 mmol/liter and blood/plas ma glucose determinati ons	--	Gender, age, smoking, educational level, marital status, socioeconomic status, and alcoholism	TB	DM was associated with the risk of pulmonary tuberculosi s	+++
Shah and Hux (2003) (11)	Canada	Retrospe ctive, cohort study	513749	Mean age: 61	---	1-12	---	TB	TB is a risk factor for death in DM patients	++++
Ponce-De- León et al. (2004) (12)	Mexico	Populat ion- based, cohort study	581	All ages	---	6.8	---	TB	TB were more in patients with diabetes than non- diabetic people	++
Dyck et al. (2007) (13)	Canada	Retrospe ctive, cohort study	2122	50-59	---	1-53	Age, gender, and BMI	TB	TB was more in patients with diabetes than non- diabetic	+++
Movahed et al. (2005) (14)	Iran	Compar ative study	845748	DM:65.8 ±11.3 Control:6 4.8±12.6	According to the International Classification of Diseases	PE: 0.7% PHT: 1.1%	Age, gender, and comorbid conditions	PE and PHT	DM was found to be significantly associated with PE and PHT	++

Continuuous of table 1.

Singla et al. (2006) (15)	Saudi Arabia	Comparative study	692		DM was diagnosed by demonstrating at least two fasting plasma glucose tests of >140 mg/dl	27.2%	---	TB	There are a higher pre-treatment bacillary load, a lower prevalence of Anti-TB drug resistance in patients with PTB-DM	++
Jick et al. (2006) (16)	USA (Massachusetts)	Case-control study	497	All ages	---	---	Age, gender, ethnicity, smoking, BMI	TB	DM and COPD are the main risk factors for TB	+++
Enomoto (2001) (17)	Japan	Case-control approach	65	Mean age: 65.4±7.8	DM:15-: FBS> 126 mg/dL and/or HbA1C > 6% IPF: clinical history, clinical examination, and HRCT of the chest	11.4%	Age, gender, smoking history, and results of physical examinations, blood examinations, and pulmonary function	IPF	DM may be a risk factor for IPF	+++
Alisjahbana et al. (2006) (18)	Indonesia	Case-control study	481	15-75 Mean age: 30	DM: measurement of FBG concentrations	13.2 %	Age, gender, and BMI	TB	DM is associated with TB in young and non-obese cases	++
Gribbin et al. (2009) (19)	UK	Case-control study	920	Mean age: 71	---	10%	Age, gender, smoking, socioeconomic status and use of prednisolone	IPF	There was a significant association between the IPF and DM	++++
WANG (2009) (20)	Taiwan	Case-control study	217		---	--	Age, gender, and BMI	TB	Type 2 DM had a negative effect on the treatment of PTB	++
Perez (2006) (21)	Mexico	Case-control study	4915	>15	Ninth version of the International Classification of Diseases (ICD-9)	-	Gender, age, and ethnicity	TB	Likely to have TB was twice in DM patients	++
Ehrlich et al. (2010) (22)	USA (California)	Retrospective, longitudinal, cohort study	77637	>18	Self-report	---	Age, gender, ethnicity, smoking, BMI, level of education, alcoholism, and outpatient visits	Pneumonia, asthma, COPD, fibrosis, pneumonia, pulmonary cancer	Frequency of pulmonary diseases was significantly higher in those with DM	++
Stevenson et al. (2007) (23)	India	Epidemiological model	18363	>25	---	14.8%	---	TB	DM is associated to TB and the diabetes frequency in urban areas is in urban than rural areas	+
Golsha et al. (2005) (24)	Iran	Cross-sectional study	162	50.15±19	---	23.05%	---	Pulmonary TB	Screening of pulmonary TB in patients DM is essential	++

WHI: Women's Health Initiative; FGL: Fasting glucose levels; COPD: Chronic obstructive pulmonary disease; IPF: Idiopathic pulmonary fibrosis; HRCT: High-resolution CTs; PE: Pulmonary embolism; PH: Pulmonary hypertension

studied articles. Eight of the reviewed studies were cohort studies, six of them were case-control, and five were comparative, cross-sectional, and retrospective. The four of the reviewed studies were on the relationship between DM and one or more pulmonary diseases. In the 17 of our reviewed studies, the samples were in advanced age; however, in two of them, the patients were of all age ranges. The five of the studies were from the United States, although there were some studies from other countries. The rate of diabetes with concomitant pulmonary diseases was different and ranged between 0.05% and 27%. The frequency of *tuberculosis (TB)* in diabetic patients was more than the other pulmonary diseases.

Discussion

Pulmonary diseases are observed among diabetic patients, and also there was an association between DM and impaired pulmonary function (25, 26). DM causes some pulmonary risk factors such as vascular diseases, which can lead to mortality in some cases. Although increased susceptibility to pulmonary tuberculosis and risk of respiratory distress syndrome in neonates has reported in diabetic patients, their relationship with DM and pulmonary diseases is not clear yet (22).

According to the Third National Health and Nutrition Examination Survey, FEV1 is lower in diabetic patients, as compared to non-diabetics patients, and there is an association between glycemic markers and FVC (4, 26, 27). The severity of diabetes is associated with the reduced pulmonary function; therefore, the mechanism leading to impaired glycemic control may lower pulmonary function (28).

DM is associated with periodic breathing and maybe as a result of sleep-disordered breathing. The prevalence rate of periodic breathing in diabetic patients is reported to be 5.4%, and reduced diffusion capacity has observed in type 2 diabetic patients (28). Also, the incidence of impaired pulmonary function was higher in patients with poorly controlled diabetes (4). The abnormal pulmonary function is observed in 73% of young, asymptomatic patients (reduction of 8–20% in FVC and FEV1) (28).

TB is a cause of mortality, and about 8.8 million new cases of TB were estimated in 2005 (29). The incidence of TB is mostly reported in patients with human immunodeficiency virus infection and diabetes (30).

Some studies showed that 10–30% of TB patients might have DM (8, 31–34). Previously, DM was known as a risk factor for TB (35, 36); however, given the improvements in the

treatment of both diseases, few studies have been done on the association between TB and DM. This issue needs to be reconsidered given the increasing rate of type 2 DM in developing countries, where TB is endemic (37). Nonetheless, there is a scarcity of studies on the association between non-diabetic hyperglycemia and tuberculosis.

Indonesia has the third highest number of patients with TB (29) and the fourth highest number of DM (37). According to a study by Alisjahbana et al., type 2 DM was observed in 13.3% of the patients with TB in Indonesia. Alisjahbana et al. examined the association between DM, severe TB, and poor response to treatment. They showed that there was a significant relationship between DM and TB treatment and that the risk of TB is associated with impaired fasting glucose and diabetes (18).

Given the possible effects of DM on the severity and outcome of TB are yet unknown, Alisjahbana et al. investigated whether DM is associated with inadequate response to TB treatment. According to their study, there was no significant relationship between sputum microscopic examination results and DM after two months. However, the number of DM patients who had TB was twice higher than the non-diabetic patients after six months; therefore, the prognosis of TB and DM is interrelated (8). Although these results were confirmed by several studies (38–41), they are inconsistent with some other studies (15, 42).

The relationship between DM and TB in diabetic and non-diabetic patients was assessed in some other studies. Although there were significant differences in symptoms of these patients (15, 42, 43), patients with DM showed a higher rate of fever and hemoptysis in a study by Restrepo et al. (33). The patients in that study were not systematically screened for DM and TB, and there were no detailed data on the possible confounding variables (33).

In another study, Alisjahbana et al. assessed the relationship between type 2 DM and TB. They showed that DM is strongly associated with positive sputum culture results because the symptoms of DM patients presented before initiation of TB treatment. Moreover, at the end of six months of DM treatment, there was no evidence of severe TB. Therefore, type 2 DM increases the risk of developing active TB. Also, confounding variables such as age, gender, nutritional status, accessibility to health care services, and comorbidity were assessed by Alisjahbana et al. According to their report, diabetic patients presented with more symptoms than non-diabetic patients (8).

Similar to the Alisjahbana et al. study, the

high rate of sputum smear positive during the first months of DM treatment was reported in a survey by Restrepo et al. (33). The treatment failure rate in Alisjahbana et al. study was 3.1% in the control group. Positive sputum culture result was observed in 5.9% of the patients who completed six months of treatment. In fact, adherence to treatment was the primary factor in the treatment of diabetic patients. According to that study, although there was an association between DM and symptoms of TB, there was no association between DM and the severity of TB. Nevertheless, DM had an adverse effect on the treatment of TB (8).

Moreover, a study on the prevalence of TB in DM patients was performed in India. The obtained results showed that the incidence of TB in patients with DM was 14.8% (range: 7.1-23.8%) and the rate of smear-positive TB due to DM was 20.2% (range: 8.3-41.9%). They also suggested that DM presents in 18.4% of adults with pulmonary TB and 23.5% of those with smear-positive TB. The incidence of smear-positive TB was 15.2% greater in urban areas, as compared to rural areas (23). The prevalence of DM among TB patients was 25% in a study performed in Mexico (12).

Although the sample size and age, as well as the definitions used for DM and TB, were different in the reviewed articles, TB was the most prevalent pulmonary disease in DM patients. Given the considerable effect of DM on TB epidemiology, prophylactic-educational programs are of great importance to prevent TB, reduce the rate of TB mortality, and improve its diagnosis and treatment.

COPD is another pulmonary disease, which might be associated with DM. According to a study by Atherosclerosis Risk in Communities and the Nurses' Health Study, the relative risk of developing type 2 DM in patients with COPD is 1.8-2.0% (28). A study by Ehrlich et al. showed that the rate of COPD was more significant in diabetic patients than non-diabetic patients, and the risk of COPD and pneumonia increased with increasing baseline glycosylated hemoglobin in patients with diabetes; however, this association was not observed in asthma and pulmonary fibrosis patients (22), these results were confirmed by other studies (7, 44). Koskinen et al. proposed that the rate of mortality due to respiratory diseases in cases with DM is higher than non-diabetic cases (44). Another study demonstrated a relationship between pulmonary disorders (such as pulmonary fibrosis, chronic bronchitis, idiopathic pulmonary fibrosis, pulmonary hypertension) and DM (20, 33, 45). Nevertheless, there is no data regarding the association between DM and pulmonary cancer

in the previous studies (46-48).

According to Moran et al., DM is the most common comorbidity in patients with cystic fibrosis, and mortality due to chronic inflammatory pulmonary disease is observed in these patients, although their relationship is not significant. Indeed, the majority of studies showed that there were no significant differences between genders with pulmonary diseases among DM patients. According to a study by Moran et al., pulmonary function in DM patients was significantly worse than the non-diabetic patients, especially in males (65 ± 24 vs. 71 ± 24 ; $P < 0.05$) (49).

According to the Moran study, the nutritional status of patients with pulmonary diseases was worse than other patients. Nutritional state plays an essential role in the treatment of DM (49). The pulmonary condition is a risk factor for diabetic patients with cystic fibrosis-related diabetes, as compared to non-diabetic patients who had cystic fibrosis (50-54). Besides, smoking and obesity are reported to be risk factors for developing both pulmonary diseases and type 2 diabetes (22, 55, 56).

According to Kornum et al., the risk of hospitalization due to pneumonia is more in both type 1 and type 2 diabetes patients with poor glycemic control (57). This result was confirmed by an in-vitro study by Pozzilli and Leslie. That study suggested a relationship between hyperglycemia and abnormalities in neutrophil function (58).

Future studies on the relationship between DM and TB are required, especially in developing countries. There are no specific recommendations on the relationship between DM and TB in WHO programs. However, screening for latent TB in patients with DM is recommended in the guidelines of American Thoracic Society (59). Screening patients with DM for TB is essential for improving care services in DM patients with concomitant TB, mainly those patients aged more than 35 years (60). There is a need for future studies on these two disorders all over the world, especially in places where the incidence of DM is increasing rapidly, and TB remains endemic. Moreover, determining the effects of glycemic control on TB treatment seems to be necessary (23).

Conclusion

Abundant evidence on the increased risk of some pulmonary diseases in diabetic patients was found. Additionally, the rate of TB was reported more than the other pulmonary disorders. Hence, screening of DM patients with pulmonary illnesses should be considered as the public health monitoring programs across world.

Furthermore, efforts to diagnose and treat DM may have a beneficial impact on controlling pulmonary diseases. Finally, conducting further studies to assess the risk of age, gender, smoking, and blood sugar levels in patients with both pulmonary diseases and DM is required.

Conflict of Interest

The authors declare no conflict of interest.

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