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Pulmonary tuberculous cavities in diabetic patients: Glycemic control is still the dominant factor despite the emerging role of metformin

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Abstract

Background: Previous studies have reported an increased risk of cavities in diabetic patients with pulmonary tuberculosis (PTB), which may be associated with poor glycemic control. Cavities have a negative impact on PTB treatment outcomes; however, the possible interaction of other potentially confounding diabetes-related variables regarding pulmonary cavities have not been fully evaluated.

Methods: We conducted a retrospective cohort study of diabetic patients with culture-proven PTB. The patients' chest X-rays (CXRs) and computed tomography (CT) scans were reviewed to assess the effects of clinical factors, glycosylated hemoglobin (HbA1c) levels, and antidiabetic agents on cavitary lesions.

Results: Among 128 diabetic PTB patients, those with pulmonary cavities on CXRs and CT scans presented younger ages, lack of metformin treatment, and significantly higher HbA1c levels than those without cavities. Multivariate logistic regression analysis revealed significantly higher HbA1c levels in patients with cavities than in those without cavities on CXRs (odds ratio [OR], 1.34; 95% confidence interval [CI], 1.12-1.61) and CT scans (OR, 1.36; 95% CI, 1.13-1.64). Patients with multiple cavities had significantly higher HbA1c levels than those with a single cavity on CT scans ($p = 0.002$). No significant differences in other variables, including metformin treatment, were noted between the groups.

Conclusion: This study suggests that despite multiple potential confounding variables, including metformin use, poor glycemic control is still the dominant risk factor for cavitary lesions in diabetic patients with PTB. Efforts to improve glycemic control in diabetic PTB patients may be of considerable value in facilitating antimycobacterial treatment.

Keywords: Diabetes mellitus; Hemoglobin A1c; Metformin; Tuberculosis

1. INTRODUCTION

Despite major advances in tuberculosis (TB) control, TB continues to be an important health issue worldwide, imposing a large disease burden, with 10.2 million incident cases, 10.1 million prevalent cases, and 1.3 million mortality cases, as reported by the 2015 Global Burden of Disease Study.[1] Among the risk factors for TB, diabetes mellitus (DM) plays an increasingly important role not only because of its impact on increasing the risk of developing active and latent TB infections[2–4] but also because of its association with poor TB treatment outcomes, including an increased risk of delayed sputum conversion, treatment failure, multidrug resistance, relapse, and mortality.[1,2,5,6]

Pulmonary cavities are not only a classic hallmark of pulmonary TB (PTB) but are also associated with a high mycobacterial burden, serving as the principle source of disease transmission,[7] drug resistance,[8] and treatment failure.[9] Therefore, because diabetic PTB patients have a significantly higher risk of cavitary lesions and multiple cavities compared with those without DM,[10,11] identifying the risk factors for cavities in diabetic PTB patients is essential for achieving the comprehensive prevention and management of PTB.

Prior studies reported that glycemic status has a positive association with cavitary lesions in diabetic PTB patients, with a higher risk of lesions in those with poor glycemic control.[10–12] Recently, metformin has received significant attention as a potential immunomodulator in PTB management because it facilitates autophagy and restricts lung tissue damage by reducing the inflammatory response.[13,14] In the report by Singhal et al, TB cavities were less commonly observed in metformin users than in those without metformin treatment.[13] However, these studies did not evaluate the possible interaction of potentially confounding variables regarding pulmonary cavities in diabetic PTB patients. To clarify these issues, we

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conducted the current study to assess the impact of clinical and DM-related factors on pulmonary cavities observed on chest X-rays (CXRs) and thoracic computed tomography (CT) scans in diabetic PTB patients.

2. METHODS

2.1. Patients

This retrospective study was conducted at two National Yang-Ming University-affiliated teaching hospitals in northern Taiwan from January 1, 2010 to December 31, 2016 and was approved by the institutional review board of National Yang-Ming University Hospital (NYMUH IRB No. 2017A030). The medical records of all patients with positive cultures for *Mycobacterium tuberculosis* from respiratory specimens (sputum, bronchoalveolar lavage, lung aspiration, or lung biopsy) were eligible for this study. Patients with extrathoracic TB, human immunodeficiency virus infection, undergoing immunosuppressant treatment, with underlying malignancies, or with concurrent pulmonary diseases, including lung cancer, pneumoconiosis, and other pulmonary infections, were excluded from the study. The results from the enrolled patients' sputum acid-fast bacilli (AFB) testing using Ziehl-Neelsen staining and their grades following CDC guidelines were also recorded.[15] Patients with grades of 3+ or 4+ were defined as having high AFB smear grades.

Further, DM patients were defined only as those (1) treated with hypoglycemic agents, (2) assigned an ICD-9 code related to DM twice or more on outpatient visits or admission, or (3) who had a fasting blood glucose concentration >126 mg/dL at two different time points. Only patients already known to have diabetes at the time of PTB diagnosis (previously known DM) and those with diabetes diagnosed concurrently with PTB (newly diagnosed DM) were enrolled. Patients diagnosed with diabetes after they were shown to have PTB were excluded from the study. In addition, glycemic status was assessed based on glycosylated hemoglobin (HbA1c) levels; therefore, only patients with HbA1c data recorded within 1 month of the PTB diagnosis were included. Disease durations of the patients diagnosed with DM and their prescribed antidiabetic agents, including metformin, other oral hypoglycemic agents, and insulin at the time of PTB diagnosis, were also recorded. Regarding the evaluated association of metformin with pulmonary cavities, patients with chronic kidney disease (CKD) stage 3b or higher were excluded because this is a contraindication for metformin use, which could have a confounding effect.[16]

Only diabetic PTB patients with pretreatment CXRs and thoracic CT scans corresponding to the positive cultures were included in the study because that CT images are more sensitive than CXRs for the detection of pulmonary pathology, including cavitary lesions of PTB.[17,18] Each patient's clinical data were compiled from electronic medical records using a standard format and included age, gender, smoking history, sputum AFB smear grade, HbA1c level, and antidiabetic agent use. All personal patient data were deidentified.

2.2. Radiographic evaluation

Two radiologists (L.K.H. and L.D.J.), both with 8 years of experience in chest imaging, were blinded to patients' clinical information and independently reviewed and interpreted the CXRs and thoracic CT scans using a standardized form. The final decision regarding the findings was achieved by consensus. Disagreements were presented to a conference consisting of the two readers and one senior radiologist (M.H.W., in practice for 25 years) for discussion, and the adjudicated reading after consensus was used as the final result.

A pulmonary cavity, as defined by the Fleischner Society, is a gas-filled space, seen as a lucency or low-attenuation area, within a nodule, mass, or area of parenchymal consolidation.[19] Therefore, cavitary lesions in the present study include cavitated nodules, cavitated mass lesions, and cavitated consolidations.

2.2.1. Chest radiography

Interpretation of the CXRs focused on pulmonary cavities, and the presence of cavities was recorded. Additionally, the radiographic disease extent was graded based on the U.S. National Tuberculosis and Respiratory Disease Association scheme, which classifies diseases as minimal, moderately advanced, or far advanced.[20]

2.2.2. Thoracic CT

All CT studies were performed using two 64-multidetector CT scanners (Brilliance 64, Philips Medical Systems, Best, The Netherlands). In addition to recording pulmonary cavity positivity, the number (single or multiple) of cavities was also evaluated because compared with CXRs, thoracic CT scans exhibit superior sensitivity and accuracy. We also assessed the presence of other findings on CT scans, including mediastinal or hilar lymphadenopathy (lymph node with a short-axis diameter > 10 mm), pleural effusion, centrilobular nodules or branching linear opacities (tree-in-bud appearance), bronchogenic spread (consolidation, or clusters of nodules in a lobe other than the lobe with the main TB lesions), location (usual or unusual), and the radiological disease distribution. Regarding the location of parenchymal abnormalities including cavities, those in the usual location were limited to or involved mainly in the apical and posterior segments of the upper lobes and superior segments of the lower lobes, while lesions limited to those involving mainly the remaining lung segments were considered unusual.[21]

2.3. Statistical analysis

The demographic and clinical characteristics of the patients are summarized as percentages for categorical variables and as the means and SDs for continuous variables. The PTB symptom and diabetic duration results are presented as medians (interquartile range). Categorical variables between the two groups were compared using Fisher's exact test. Continuous variables between two groups were compared using independent Student's *t* test. The Mann–Whitney *U* test was used to compare the PTB symptom and diabetic durations between the two groups. A multivariate logistic regression analysis was performed to evaluate the independent risk factors of pulmonary cavities in diabetic PTB patients. Statistical significance was defined as $p < 0.05$ (two-tailed). The statistical analysis was performed using SPSS software for Windows (version 22; IBM-SPSS, Chicago, IL, USA).

3. RESULTS

3.1. Patient characteristics

In total, 1671 patients presented culture-proven PTB during the 6-year study period, and 377 of these had diabetes at the time of PTB diagnosis. Among these 377 patients, 159 without corresponding thoracic CT images when diagnosed with PTB and 17 patients lacking HbA1c data within one month of the PTB diagnosis were excluded. After excluding patients who used immunosuppressive agents, were HIV positive, had underlying malignancies, had CKD stage 3b or higher, or had concurrent lung diseases, 128 diabetic PTB patients (105 men and 23 women) with associated CXRs and thoracic CT scans were enrolled in this study (Fig. 1).

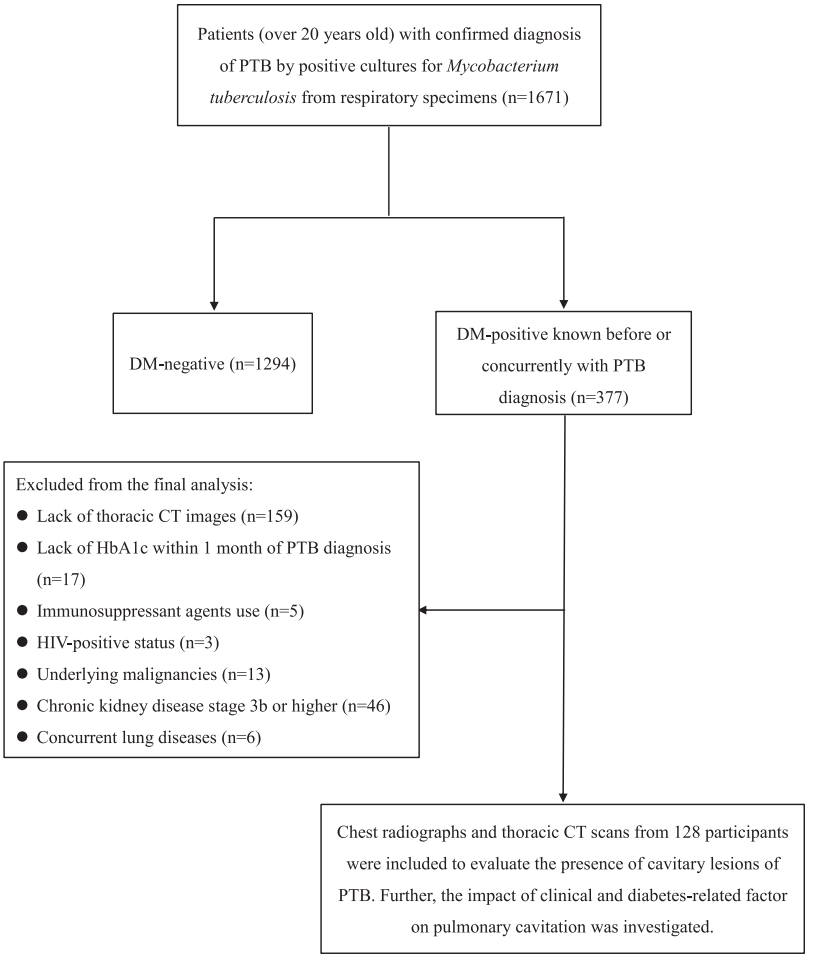

Fig. 1 Flow-chart for the enrollment of diabetic pulmonary tuberculosis (PTB) patients in current study.

3.2. Comparison of clinical characteristics and radiological disease severity of patients with and without pulmonary cavities on CXRs

Among the 128 patients, 43 (33.6%) had pulmonary cavities on CXRs (Fig. 2) and 85 had no pulmonary cavities on CXRs. The clinical characteristics and radiological severity of disease in these two groups are shown in Table 1. High sputum AFB smear grades were more commonly observed in the patients presenting with cavities on CXRs ($p < 0.001$). In the univariate analysis, patients with cavities were significantly associated with younger age ($p = 0.003$), higher HbA1c levels ($p < 0.001$), shorter diabetes duration ($p = 0.01$), and less metformin use ($p = 0.004$) than patients without cavities. After adjusting for age, diabetes duration and metformin use in the multivariate analysis, only the HbA1c level (odds ratio [OR], 1.34; 95% confidence interval [CI], 1.12-1.61; $p = 0.001$) remained significantly higher in patients with pulmonary cavities than in those without cavities.

3.3. Comparison of clinical characteristics and radiological findings of patients with and without pulmonary cavities on thoracic CT scans

Pulmonary cavities on thoracic CT scans were noted in 57 of the 128 patients (44.5%). Table 2 summarizes the clinical characteristics and radiological findings. Thoracic CT findings showed that tree-in-bud appearance ($p = 0.001$), bronchogenic spreading ($p < 0.001$), predominant lesions in unusual locations ($p < 0.001$), and diseases involving all lobes ($p = 0.037$) were more common in patients with cavities. High sputum AFB smear grades were also more frequently observed in patients with cavities on their CT scans ($p < 0.001$). Regarding the correlation between clinical factors and cavitary lesions in the univariate analysis, patients with cavities were more likely to be younger ($p = 0.001$), have higher HbA1c levels ($p < 0.001$), have shorter diabetes durations ($p = 0.002$), and use less metformin ($p = 0.003$) than patients without cavities. After adjusting for age, diabetes duration, and metformin use in the multivariate analysis, only higher HbA1c levels (OR, 1.36 [95% CI, 1.13-1.64]; $p = 0.001$) remained significantly associated with a higher risk of pulmonary cavities on thoracic CT scans.

The clinical characteristics and imaging findings for patients with pulmonary cavitary lesions on CT scans were further stratified by the number of cavities, and the results are summarized in Table 3. Compared with patients with a single cavity, those with multiple cavities (Fig. 3) were more likely to have bronchogenic spreading ($p = 0.035$) and diseases involving all lobes ($p = 0.045$) on thoracic CT scans. Regarding the association of clinical factors and number of cavities, the presence of multiple cavities was only significantly associated with higher HbA1c levels ($p = 0.002$).

4. DISCUSSION

The most relevant finding of our study is that glycemic status has the most significant impact on the pulmonary cavities of

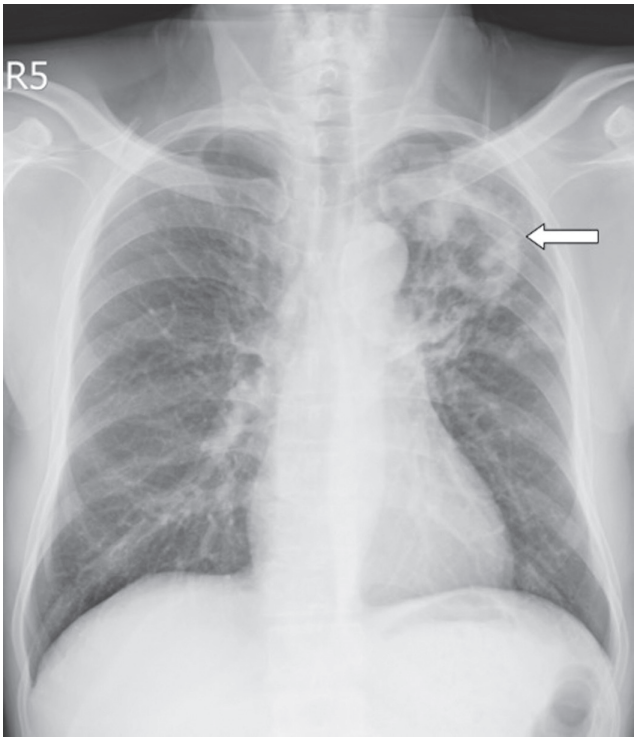

Fig. 2 Culture-proven pulmonary tuberculosis in a 53-year-old man, who had a history of diabetes mellitus and a glycosylated hemoglobin (HbA1c) level of 10.4% at the time of tuberculosis diagnosis. Chest radiograph shows a cavitary mass (arrow) and satellite lesions with small ill-defined nodules and infiltrates in the left upper lobe of the lung.

diabetic PTB patients; individuals with cavitary lesions on both CXRs and thoracic CT scans have inferior glycemic control to those without cavities.

TB cavities arise from central caseation and subsequent rupture of granulomas (tubercles). In diabetic patients, immune dysfunction driven by hyperglycemia may lead to the generation of TB cavities.[22] Furthermore, while TB cavities are associated with smear positivity, a higher bacillary burden in the sputa is observed in diabetic patients compared with those without DM.[23] In the current study, we further demonstrated that diabetic PTB patients with cavities had a significantly higher risk of having high PTB smear grades in their sputa than those without cavities. Additionally, patients with multiple cavities had a trend to show high sputum PTB smear grades than those with a single cavity. Moreover, as bronchogenic spreading with consolidation or clusters of nodules being the CT predictive with smear-positive active PTB,[24] our study population with CT cavities were more likely to have these findings, especially in those with multicavities. Therefore, identifying and then eliminating the risk factors of cavitary diabetic PTB is essential to reduce onward TB transmission.

Several previous studies have identified that diabetic patients with poor glycemic control have an increased risk of TB cavities,[10–12] and our results further confirmed the link between glycemic status and pulmonary cavities in diabetic PTB patients after adjustment for clinical and other DM-related factors. Furthermore, compared with subjects with a single cavity on CT, a significantly higher HbA1c level was also found in those with multiple cavities on CT in our study. Notably, regarding multidrug-resistant TB and extensively drug-resistant TB, cavitary lesions not only generate an increased risk of drug-resistant TB strains but also complicate the disease eradication.[8] Pulmonary cavities are negatively associated with sputum

Table 1

Clinical characteristics and radiological disease severity in diabetic PTB patients with and without cavities on CXRs

Variables	With cavity (N = 43)	Without cavity (N = 85)	*p*	Odds ratio[a] (95% CI)
General demographics				
Age, years	65.0 ± 13.6	72.9 ± 13.9	0.003[b]	NS
Gender, male/female (N, %)	37/6 (86.0%/14.0%)	68/17 (80.0%/20.0%)	0.400[c]	…
History of smoking (N, %)	19 (44.2%)	31 (36.5%)	0.398[c]	…
TB symptoms duration, mo[d]	1.0 (0.5-3.0)	1.0 (0.25-2.0)	0.289[e]	…
High sputum AFB smear grade (N, %)	24 (55.8%)	19 (22.4%)	<0.001[c]	…
Diabetes-related factors				
HbA1c, %	10.54 ± 2.27	8.36 ± 2.40	<0.001[b]	1.34 (1.12-1.61)
Diabetes duration, mo[d]	3.0 (0-60.0)	36.0 (0-82.5)	0.01[e]	NS
Newly diagnosed diabetes (N, %)	20 (46.5%)	25 (29.4%)	0.056[c]	…
Antidiabetic agents (N, %)				
Metformin	10 (23.3%)	42 (49.4%)	0.004[c]	NS
Other OHAs	21 (48.8%)	40 (47.1%)	0.849[c]	…
Insulin	1 (2.3%)	7 (8.2%)	0.192[c]	…
Radiological severity of disease[f]			0.312[c]	…
Minimal (N, %)	10 (23.3%)	31 (36.5%)	…	…
Moderately advanced (N, %)	28 (65.1%)	45 (52.9%)	…	…
Far-advanced (N, %)	5 (11.6%)	9 (10.6%)	…	…

[a]Multivariant regression analysis. Covariables in the multivariate logistic regression analysis: age, HbA1c, diabetes duration and metformin (±).

[b]Independent Student's *t* test.

[c]Fisher's exact test.

[d]Data are medians with interquartile ranges in parentheses.

[e]Mann-Whitney *U* test.

[f]Minimal = an area less than that above a horizontal line across the 2nd chondrosternal conjunction of one lung; Moderately advanced = an area more than minimal lesions but less than one entire lung; Far advanced = an area equivalent to or greater than one lung.

CI = confidence interval; CXRs = chest X-rays; DM = diabetes mellitus; HbA1c = glycosylated hemoglobin; NS = no significance; OHAs = oral hypoglycemic agents; PTB = pulmonary tuberculosis.

Table 2

Clinical characteristics and radiological findings in diabetic PTB patients with and without cavities on thoracic CT scans

Variables	With cavity (N = 57)	Without cavity (N = 71)	*p*	Odds ratio[a] (95% CI)
General demographics				
Age, years	65.8 ± 14.3	73.8 ± 13.3	0.001[b]	NS
Gender, male/female (N, %)	50/7 (87.7%/12.3%)	55/16 (77.5%/22.5%)	0.133[c]	…
History of smoking (N, %)	24 (42.1%)	26 (36.6%)	0.527[c]	…
TB symptoms duration, mo[d]	1 (0.5-2.0)	0.5 (0.25-2.0)	0.143[e]	…
High sputum AFB smear grade (N, %)	32 (56.1%)	11 (15.5%)	<0.001[c]	…
Diabetes-related factors				
HbA1c, %	10.27 ±2.62	8.15 ± 2.11	<0.001[b]	1.36 (1.13-1.64)
Diabetes duration, mo[d]	6.0 (0-45.0)	50.0 (0-86.0)	0.002[e]	NS
Newly diagnosed diabetes (N, %)	25 (43.9%)	20 (28.2%)	0.065[c]	…
Antidiabetic agents (N, %)				
Metformin	15 (26.3%)	37 (52.1%)	0.003[c]	NS
Other OHAs	27 (47.4%)	34 (47.9%)	0.953[c]	…
Insulin	3 (5.3%)	5 (7.0%)	0.679[c]	…
Other CT findings				
Lymphadenopathy (N, %)	10 (17.5%)	12 (16.9%)	0.924[c]	…
Pleural effusion (N, %)	12 (21.1%)	23 (32.4%)	0.152[c]	…
Tree-in-bud appearance (N, %)	49 (86.0%)	43 (60.6%)	0.001[c]	…
Bronchogenic spreading (N, %)	48 (84.2%)	34 (47.9%)	<0.001[c]	…
Unusual location predominant (N, %)[f]	45 (78.9%)	32 (45.1%)	<0.001[c]	…
All lobes involvement (N, %)	28 (49.1%)	22 (31.0%)	0.037[c]	…

[a]Multivariant regression analysis. Covariables in the multivariate logistic regression analysis: age, HbA1c, diabetes duration, and metformin (±).
[b]Independent Student's *t* test.
[c]Fisher's exact test.
[d]Data are medians with interquartile ranges in parentheses.
[e]Mann–Whitney *U* test.
[f]Lesions limited to or involving mainly the anterior segments of the upper lobes, the right middle lobe, the lingular segment, and basal segments of the lower lung lobes.
CI = confidence interval; CT = computed tomography; DM = diabetes mellitus; HbA1c = glycosylated hemoglobin; NS = no significance; OHAs = oral hypoglycemic agents; PTB = pulmonary tuberculosis.

Table 3

Clinical characteristics and radiological findings in diabetic PTB patients with multiple cavities or a single cavity on thoracic CT scans

Variables	Multiple cavities (N = 31)	Single cavity (N = 26)	*p*
General demographics			
Age, years	64.0 ± 14.1	68.0 ± 14.5	0.297[a]
Gender, male/female (N, %)	26/5 (83.9%/16.1%)	24/2 (92.3%/7.7%)	0.334[b]
History of smoking (N, %)	12 (38.7%)	12 (46.2%)	0.571[b]
TB symptoms duration, mo[c]	1.0 (0.25-3.0)	1.0 (0.5-2.0)	0.935[d]
High sputum AFB smear grade (N, %)	21 (67.7%)	11 (42.3%)	0.054[b]
Diabetes-related factors			
HbA1c, %	11.22 ± 2.59	9.14 ± 2.19	0.002[a]
Diabetes duration, mo[c]	4.0 (0-35.0)	12.5 (0-60.0)	0.466[d]
Newly diagnosed diabetes (N, %)	14 (45.2%)	11 (42.3%)	0.829[b]
Antidiabetic agents (N, %)			
Metformin	7 (22.6%)	8 (30.8%)	0.484[b]
Other OHAs	14 (45.2%)	13 (50.0%)	0.716[b]
Insulin	2 (6.5%)	1 (3.8%)	0.661[b]
Other CT findings			
Lymphadenopathy (N, %)	6 (19.4%)	4 (15.4%)	0.695[b]
Pleural effusion (N, %)	7 (22.6%)	5 (19.2%)	0.757[b]
Tree-in-bud appearance (N, %)	28 (90.3%)	21 (80.8%)	0.301[b]
Bronchogenic spreading (N, %)	29 (93.5%)	19 (73.1%)	0.035[b]
Unusual location predominant (N, %)[e]	25 (80.6%)	20 (76.9%)	0.731[b]
All lobes involvement (N, %)	19 (61.3%)	9 (34.6%)	0.045[b]

[a]Independent Student's *t* test.
[b]Fisher's exact test.
[c]Data are medians with interquartile ranges in parentheses.
[d]Mann–Whitney *U* test.
[e]Lesions limited to or involving mainly the anterior segments of the upper lobes, the right middle lobe, the lingular segment, and basal segments of the lower lung lobes.
CT = computed tomography; DM = diabetes mellitus; HbA1c = glycosylated hemoglobin; OHAs = oral hypoglycemic agents; PTB = pulmonary tuberculosis.

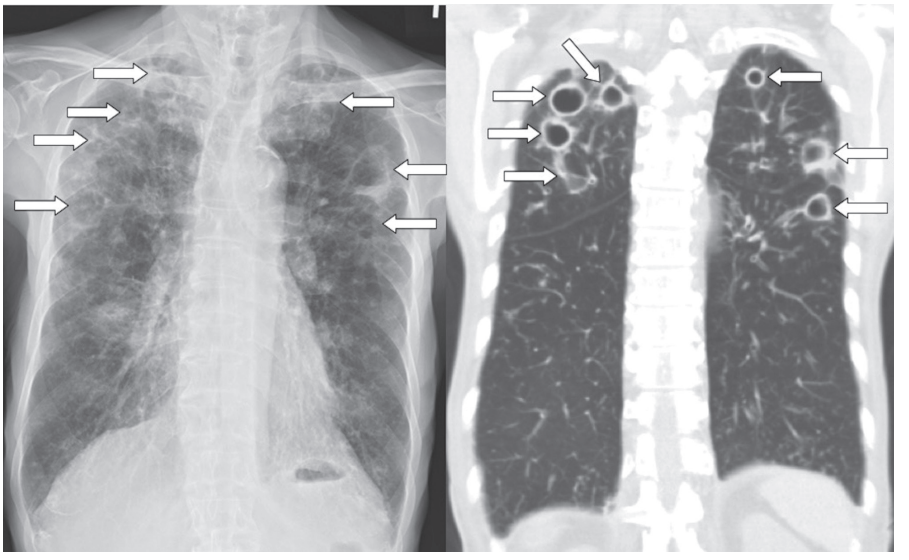

Fig. 3 Culture-proven pulmonary tuberculosis in an 88-year-old man, who had a history of diabetes mellitus and a glycosylated hemoglobin (HbA1c) level of 10.7% at the time of tuberculosis diagnosis. Chest radiograph (A) and coronal thoracic CT image (B) show multiple cavitary lesions (arrows) in bilateral lungs.

culture conversion and treatment outcomes of drug-resistant PTB,[25–27] and the heteroresistance profiles in clonal populations of TB strains in patients with multiple lung cavities can further complicate disease management.[28] Accordingly, hyperglycemia and the consequent increased risk of TB cavities in diabetic patients may hamper PTB treatment. Because improved blood glucose control is associated with radiological resolution of pulmonary abnormalities,[12] appropriate glycemic control is of critical value to achieve successful treatment of PTB.

Our study further investigated the impact of the use of metformin on pulmonary cavities in diabetic TB patients. Metformin, as a first-line treatment and the most frequently prescribed medication for DM, has received significant attention as a candidate immunomodulator in TB.[14] Recent studies showed that adjuvant metformin use was associated with the lower risks of TB and relapsed disease in diabetic patients,[29–31] and was correlated with a higher rate of 2-month sputum culture conversion in cavitary PTB patients with DM.[32] In addition, a significantly lower mortality rate was noted in diabetic PTB patients using metformin than in those not using metformin,[13,33] and compared with PTB patients without DM, metformin users showed the same risk of mortality.[33] The underlying pathogenesis of PTB cavity formation may be associated with severe tissue hypoxia and uncontrolled proteolytic destruction presenting with hypoxia-inducible factor (HIF)-1α accumulation and elevated matrix metalloproteinase (MMP) concentrations in human lung tissues,[34,35] and metformin has been shown to inhibit HIF-1α and MMP expression in vitro.[36,37] One recent study further demonstrated the association between metformin use and decreased plasma MMP levels in diabetic PTB patients.[38] However, our results disagree with those reported by Singhal and colleagues;[13] in our multivariate analysis, there was no significant difference regarding the use of metformin in diabetic PTB patients with and without pulmonary cavities after adjusting for HbA1c. In fact, a significantly lower HbA1c level was found in metformin users than in those without metformin treatment in our populations (8.28 ± 2.13 vs 9.65 ± 2.70; $p = 0.003$). Accordingly, the current study suggests that the correlation of metformin use with decreased pulmonary cavities shown in the univariate analysis may be due to improved glycemic control rather than the possible immunomodulatory effect of metformin. Therefore, the potential role of metformin as immunomodulators to decrease pulmonary cavities of diabetic PTB deserves further study with a larger population. Moreover, lack of promising preclinical result regarding the adjunctive sterilizing activity of metformin against TB,[39] and the possible drug–drug interactions between metformin and anti-TB agents have been reported in previous studies.[40,41] Therefore, administering individualized antidiabetic regimens to achieve appropriate glycemic control and the consequent decreased risk of cavitary lesions may be more pragmatic in managing diabetic PTB patients.

This study has some limitations. First, the retrospective nature, limited sample size, and highly selected sample with excluding 159 potential candidates lacking CT images of diabetic patients may have introduced selection bias, which could potentially affect our conclusions, including the possible misinterpretation of the effects of metformin on TB cavities. Further studies with large population are needed to clarify these issues. Second, the implications of our findings may not be generalizable to areas or countries without endemic TB. Third, various clinical scenarios may result in falsely elevated or falsely lowered HbA1c values,[42] which may have confounded our results. Finally, the *M. tuberculosis* strains were not studied. Previous research has indicated that the strain of *M. tuberculosis* might affect the radiological findings of PTB, including pulmonary cavities.[43]

In conclusion, our study shows that after adjusting for clinical factors and antidiabetic agent use, including metformin, poor glycemic control is associated with an increased risk of pulmonary cavities on both CXRs and thoracic CT scans. Compared with patients with no cavities or a single cavity on thoracic CT scans, those with multiple cavities had significantly inferior glycemic control. Given the link between DM and TB and the significant association between poor glycemic control and pulmonary cavities, routine bidirectional screening for these two diseases should be emphasized as being essential, and appropriate glycemic control in diabetic PTB patients is of considerable value in facilitating antimycobacterial treatment.

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