

Performance of computed tomography versus chest radiography in patients with pulmonary tuberculosis with and without diabetes at a tertiary hospital in Riyadh, Saudi Arabia

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Background: Prior research suggests that diabetes mellitus (DM) is associated with increasing risk for developing cavitary lung disease in patients with pulmonary tuberculosis (TB). Additionally, chest computed tomography (CT) scan may be more sensitive than chest X-ray in detecting cavitary disease in such patients. The aim of this study was to compare the performance of chest CT to chest X-ray in detecting cavitary lung disease and to compare the frequency of cavities between TB patients with DM and without DM.

Patients and methods: We conducted a retrospective cohort study at King Fahad Medical City, Riyadh, Saudi Arabia, from January 2004 to December 2015. We included patients aged 18 years and older with a positive sputum culture for *Mycobacterium tuberculosis*, and their medical charts were reviewed from admission to discharge.

Results: Of the 133 patients who met the inclusion criteria, 38 (28.6%) patients were known to have DM and were compared with 95 (71.4%) patients without DM. DM patients with glycosylated hemoglobin (HbA1c) >6.5% had significantly more cavitary lesions when compared to all patients (with or without DM) with HbA1c <6.4% and/or random blood sugar <200 mg/dL. Furthermore, CT was able to detect lung cavities in 58.8% of the patients who had negative chest X-ray findings for cavities.

Conclusion: The presence of lung cavities was significantly associated with the presence of DM and levels of HbA1c in patients with pulmonary TB. CT scan in those with normal radiography increased the detection of cavities.

Keywords: diabetes, pulmonary tuberculosis, lung cavities, computed tomography

Introduction

The association between tuberculosis (TB) and diabetes mellitus (DM) has been described as co-epidemic. With the increasing rates of diabetes prevalence worldwide especially in countries with high burdens of TB, it is estimated that the number of individuals with both TB and DM will increase dramatically in the upcoming years.¹ Patients with DM are at greater risk for developing active TB,^{2,3} with the largest meta-analysis to date demonstrating that diabetic patients are 3.1 times more likely to develop TB than patients without diabetes.³ DM not only increases the risk of TB infection but also contributes to increased severity and poor treatment outcomes.⁴ When adjusting for comorbid conditions, DM patients are more likely to have higher rates of complications of TB treatment, such as prolonged sputum culture conversion, risk of relapse after treatment completion, and death.^{5,6}

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Saudi Arabia is one of the top 10 countries worldwide for the highest age-adjusted prevalence of DM with 24% of the population estimated as living with DM.⁷ In 2015, the total number of new cases of pulmonary TB in Saudi Arabia was 2,505. Of the country's 20 regions, Riyadh region is the most populous and has a TB incidence rate of 7.41 cases/100,000.⁸ Despite the co-prevalence of DM and TB in Saudi Arabia, comparative studies of TB individuals with and without DM are limited. For instance, one study from Sahary Hospital in Riyadh examined a cohort of TB patients admitted between 1998 and 1999; DM was significantly associated with persistent sputum positivity after 2 months of treatment, and regression analysis found that age and disease burden (number of bacilli in pretreatment sputum and cavitory lung disease by chest X-ray) were the overall dominant predictors of delayed microbiological response to treatment.⁹ Since the time of that study, and in important contrast to other TB endemic settings, diagnosis and management of TB in Riyadh have increasingly involved the use of chest computed tomography (CT) scan. Relatedly, guidelines suggest extended treatment duration to 9 months for drug-susceptible TB in patients who fail to convert their sputum to negative at 2 months, particularly in those with cavitory lung disease or comorbid conditions such as DM.¹⁰ In some studies, DM has been associated with higher rates of cavitory disease as compared with patients without diabetes.^{11,12} Additionally, chest CT scan may be more sensitive for detecting cavitory lung disease in TB patients than conventional chest X-ray.

We therefore sought to study the performance of chest CT compared to X-ray for detecting cavitory lung disease and whether cavities were more common in patients with DM-TB than in patients without DM-TB. A single-center retrospective cohort study was undertaken at a large referral hospital in the central region of Saudi Arabia, given the routine screening for DM among all TB patients and the access to chest CT findings.

Patients and methods

Subjects

A retrospective cohort analysis was performed among patients who were diagnosed with culture-positive pulmonary TB during January 1, 2004 (the operational date of the hospital) to December 31, 2015, in King Fahad Medical City, Riyadh, Saudi Arabia. Data were collected from all patients aged ≥ 18 years with a positive sputum culture for *Mycobacterium tuberculosis*.

Data collection and statistics

In patients meeting the above criteria, a detailed and systematic chart review was performed in the medical records for demographics (age and gender), prior TB history including prior TB treatment regimens, site of TB disease (pulmonary, central nervous system, lymph node, bone/joint, genitourinary, or others), medical comorbidities (DM, HIV, chronic kidney disease, liver disease, smoking, alcohol, or injection drug use), current chest X-ray or CT abnormalities, and baseline laboratory values including complete blood counts, chemistries, random blood sugar (RBS), liver function tests, erythrocyte sedimentation rate (ESR), glycosylated hemoglobin (HbA1c) on pre- and post-TB therapy, and CD4⁺ cell count if HIV infected. All medications were documented including anti-DM medications.

Patients were categorized into the following two groups: patients with DM and patients without DM. DM status was documented based on chart diagnosis and corroborated with laboratory values. Clinical outcomes were defined as the presence of cavities detected by CT scan. We examined the distribution of our data for skewness. We used univariate analysis to describe the sample characteristics by presenting mean and standard deviation (SD) for normally distributed continuous measures, median and interquartile ranges (IQR) for continuous measures that were not normally distributed, and frequencies and percentages for categorical measures. We also used Student's *t*-test or Kruskal-Wallis test to compare mean or median, respectively, and chi-square tests to compare proportions between DM patients and non-DM patients, as well as patients with cavities and without cavities. All tests of significance were two sided, and we set the α level to 0.05. All statistical analyses were performed using SPSS 24.0 (IBM Corporation, Armonk, NY, USA).

Ethical approval

The protocol was approved by the Ethical Review Committee at King Fahad Medical City and the University of Virginia, and written consent was waived by the Ethical Review Committee, as the majority of subjects were previously discharged and unavailable to be contacted. Moreover, as data were deidentified, patient confidentiality was maintained.

Results

During the study period, a total of 133 patients with positive sputum culture for *M. tuberculosis* were detected from the medical charts available for review. Of the 133 patients, 38 (28.6%) patients were known to have DM and 95 (71.4%) patients did

not have DM. Gender distribution, extrapulmonary infection, and the proportion of individuals with positive sputum smear results prior to treatment initiation were similar in both DM and non-DM groups (Table 1). DM patients were older than non-DM patients with the mean age of 58 ± 18 vs 41 ± 22 years, respectively ($P < 0.01$). Twenty of the 29 (68.9%) patients with diabetes were older than 60 years. In addition, patients with DM had more pulmonary cavities than patients without DM (17 [44.7%] vs 23 [24.2%], respectively, $P = 0.02$). As expected, DM patients had a higher median RBS level than non-DM patients (198.0 mg/dL [144.0–288.0] vs 95.4 mg/dL [86.4–109.8], $P < 0.01$). Thirty-one (81%) DM patients had HbA1c levels $> 6.5\%$ with a median level of 7.9% (7.2–11.0). Six patients with undocumented DM had HbA1c levels tested; five patients were found to be prediabetic (HbA1c 5.7–6.4%), but chart review did not reveal the indication for requesting HbA1c, and none were started on anti-DM treatment. Ultimately, 18 (50.0%) DM patients were started on insulin, 10 (23.0%) on metformin, and three (8.3%) on other oral hypoglycemic agents.

We compared patients with cavities (40 [30.1% of total population]) detected by any radiography method with patients with no cavities (93 [69.9%]) and found no significant difference between the two groups with regard to gender or presence of extrapulmonary disease. However, patients with cavitory disease (31 [42.5%]) were more likely to have baseline sputum smear positivity than patients without cavitory disease (45 [48.4%], $P < 0.01$, Table 2). Additionally, the prevalence of DM was significantly greater in patients

with cavities (17 [42.5%]) than in patients without cavities (21 [22.6%], $P = 0.02$, Table 2). When patients with HbA1c testing were examined alone, in 40 patients who had cavities, the median HbA1c level was 8.2% (7.1–12.0) pretreatment (Figure 1). We did not have enough data to find a significant difference in median HbA1c between patients with cavities and patients without cavities. However, the proportion of cavities was significantly greater in patients with HbA1c $> 6.5\%$ (16 [52.0%]) than in those with both HbA1c $< 6.4\%$ and/or RBS < 200 mg/dL (24 [27.0%], $P = 0.03$).

We then performed a sub-analysis in 38 patients with DM to observe the prevalence of cavities in this group. Somewhat surprisingly, those with cavitory disease were significantly younger (mean age = 50 years, SD = 15) compared to those without cavitory disease (mean age = 64, SD = 17, $P = 0.01$, Table 3). The median HbA1c was also greater in patients with cavitory disease than in those without cavitory disease ($P = 0.20$, Table 3).

We analyzed 36 patients who had radiological evidence of cavitory lesions and who underwent both chest CT and X-ray. Of these patients, 21 (58.3%) patients had negative X-ray but positive CT for cavities (Table 4). Figures 2 and 3 are the examples of a patient with a negative X-ray and positive CT scan for a cavitory lesion.

Of the 38 patients with DM, only 12 patients had HbA1c levels measured before and after treatment, but in these patients, there was a statistically significant improvement in HbA1c following anti-TB treatment ($P < 0.01$) (Figure 4). Regarding the time for smear conversion in days, there was

Table 1 Patients' demographics

	Characteristic, n (%)		
	Diabetes, 38 (28.6)	No diabetes, 95 (71.4)	P-value
Age, years (mean \pm SD)	58 \pm 18	41 \pm 22	<0.01
Female	16 (42.1)	40 (42.1)	>0.99
Extrapulmonary disease	7 (18.4)	12 (12.6)	0.42
Cavities	17 (44.7)	23 (24.2)	0.02
Random blood sugar (mg/dL), median (IQR)	198.0 (144.0–288.0)	95.4 (86.4–109.8)	<0.01
HbA1c (mmol/mol%), median (IQR)	7.9 (7.2–11.0)	5.9 (5.6–6.1) ^a	0.01
Smear positive	22 (57.9)	54 (56.8)	>0.99

Note: ^aSix patients had HbA1c levels tested once during admission, and no documentation was noted for the indication.

Abbreviations: HbA1c, glycated hemoglobin; IQR, interquartile range; SD, standard deviation.

Table 2 Characteristics of patients with and without cavities

	Characteristic, n (%)		
	Cavity, 40 (30.0)	No cavity, 93 (70.0)	P-value
Age (years), mean \pm SD	42 \pm 19	46 \pm 23	<0.29
Female	26 (65.0)	42 (45.2)	0.34
Extrapulmonary disease	3 (7.5)	16 (17.2)	0.18
Smear positive	31 (77.5)	45 (48.4)	<0.01
DM	17 (42.5)	21 (22.6)	0.02
Random blood sugar (mg/dL), median (IQR)	111.6 (90.0–181.8)	104.4 (86.4–124.2)	0.02

Abbreviations: DM, diabetes mellitus; IQR, interquartile range; SD, standard deviation.

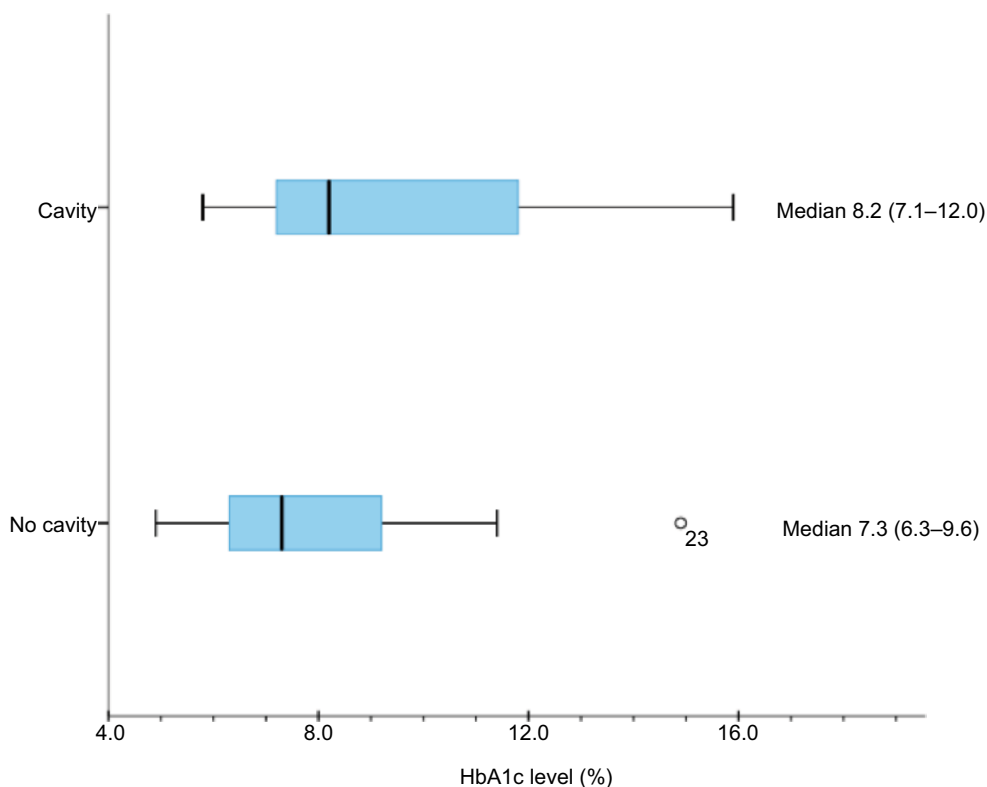


Figure 1 Median HbA1c level (%) for patients with and without cavities.
Abbreviation: HbA1c, glycated hemoglobin.

Table 3 DM patients' characteristics among those with and without cavities

	Characteristic, n (%)		P-value
	Cavity, 17 (44.7)	No cavity, 21 (55.3)	
Age (years), mean \pm SD	50 \pm 15	64 \pm 17	0.01
Female	5 (29.4)	11 (52.4)	0.20
Insulin	10 (58.8)	8 (38)	0.33
Random blood sugar (mg/dL), median (IQR)	238 \pm 112	216 \pm 108	0.60
HbA1c (mmol/mol), median (IQR)	8.6 (7.6–12.6)	7.6 (6.6–10.7)	0.20
Smear positive	12 (70.6)	10 (47.6)	0.20

Abbreviations: DM, diabetes mellitus; HbA1c, glycated hemoglobin; IQR, interquartile range; SD, standard deviation.

Table 4 All patients who received both CT and CXR with radiological evidence of cavity

	CXR result of cavity, N (%)		
	No	Yes	Total
CT result of cavity, n (%)			
No	0 (0)	2 (13.3)	2 (5.6)
Yes	21 (100)	13 (86.7)	34 (94.6)
Total	21 (58.3)	15 (41.7)	36 (100)

Abbreviations: CT, computed tomography; CXR, chest X-ray.

a wide range of reporting yet no significant differences were found between the DM and non-DM patients (31 ± 27 vs 27 ± 34 days; $P=0.69$). In addition, there were no follow-up data on 67 patients. Of those with traceable outcome, 36 (94.7% of all DM) patients were with DM. Of the 36 patients

with DM, only one patient died, four patients were lost to follow-up after completing some duration of treatment, and 31 patients were cured. Importantly, however, all patients received a total duration of 9-months' therapy when cavities were detected via imaging.

Discussion

In the present study, patients with pulmonary TB infection who had DM had more pulmonary cavities than patients without DM. In addition, diabetes patients with HbA1c $>6.5\%$ were significantly more likely to have cavitory lesions than all patients (with or without DM) with HbA1c $<6.4\%$ and/or RBS <200 mg/dL. Importantly, our results also demonstrated that CT was able to detect lung cavities in more than

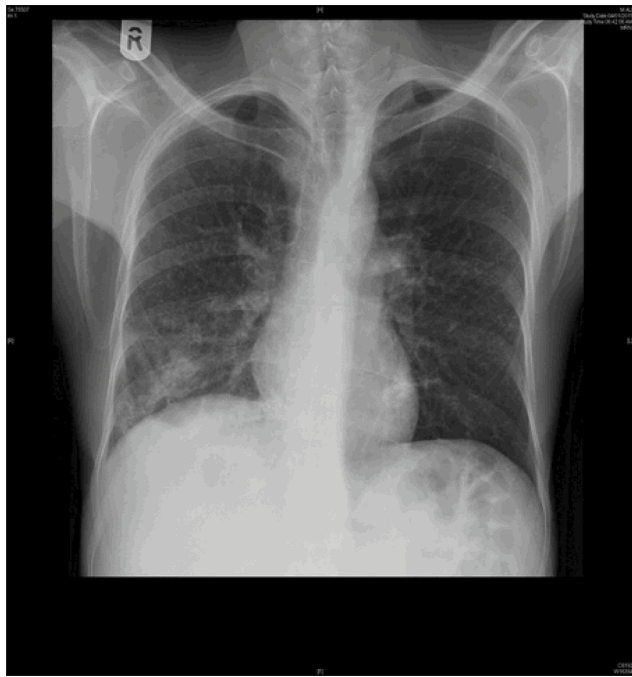


Figure 2 Chest X-ray originally read as no clear evidence of cavity.

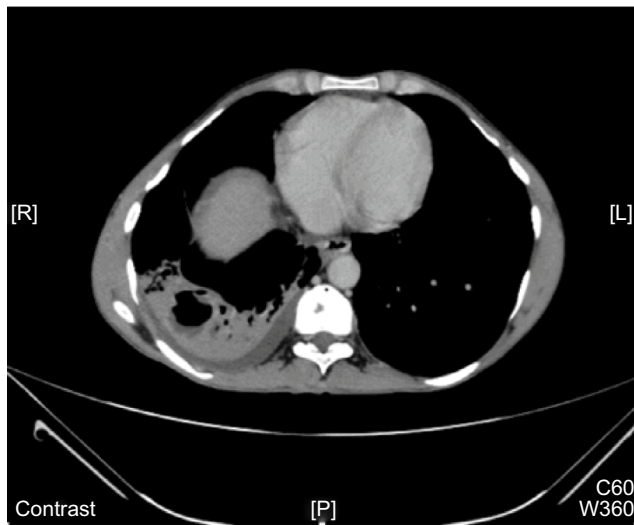


Figure 3 CT chest of the same patient in Figure 2 with evidence of cavity.
Abbreviation: CT, computed tomography

half (58.3%) of the patients who were not reported to have a cavity by chest X-ray.

Several studies have suggested that patients with pulmonary TB and DM are more likely to have cavitory lung disease than patients without DM.^{12–15} However, other studies could not demonstrate this association.^{16–18} In our study, the prevalence of lung cavities was significantly greater in DM, but we believe that the enhanced detection by CT led to this stronger association. Similar to past research, the degree of hyperglycemia was also associated with the presence of lung

cavities.¹¹ Our findings align with those by Chiang et al,¹⁹ who found the relative risk of cavitory disease increased with the higher HbA1c, reporting that when compared with patients without DM, the risk for cavitory disease is 0.87 (relative risk [RR] =0.87, 95% CI =0.46–1.62) for patients with DM with HbA1c <7%, 1.84 (95% CI 1.20–2.84) for patients with DM with HbA1c 7–9%, and 3.71 (95% CI 2.64–5.22) for patients with DM with HbA1c >9%.

Similarly, chest X-ray has been read as normal in 10–15% of symptomatic patients with later biopsy-proven infiltrative lung disease.²⁰ Other studies show that CT scan of the chest is a reliable diagnostic tool to detect and assess lung parenchymal diseases in pulmonary TB with a sensitivity of 97% and a specificity of 86.7%, yielding a positive predictive value of 94.2% and a negative predictive value of 97%.^{21,22} In our study of patients from Riyadh, more than half of those with cavities proven by CT scan had normal chest X-ray, with direct clinical implications on the duration of TB treatment. Common practice in Riyadh advises clinicians to treat TB patients with cavities visible by CT scan for 9 months. While our analyses were not designed to examine the effect of treatment duration on outcome, patients with cavitory disease had favorable outcomes. While CT scan may be of less importance relative to improving other resources and infrastructure in TB endemic areas, our findings suggest that in settings with access to CT scan, routine utilization may alter management. Such individualization of treatment duration may be particularly important in DM/TB patients for whom relapse and treatment failure are of greater concern.^{14,23}

Several limitations for our study should be noted. First, because data were collected from hospital charts, there was limited information about historical features that were relevant to this study and may be related to the inadequacy of chart documentation (eg, immunosuppressing conditions, smoking history, alcohol use, and illicit drug use). We were unable to follow-up patients through their visits to primary health clinics within the city or their later treatment outcomes. The temporal association between the development of DM and the development of TB was also not assessed. Second, during TB treatment, not all patients had documentation of changes in DM therapy, or if they had received HbA1c testing during or after completing TB therapy. Third, because routine sputum cultures were not taken during treatment, we were not able to make associations about the effect of DM treatment on TB disease outcome, as has been suggested with emerging reports of independent tuberculocidal effects of the anti-DM medication metformin.²⁴ Finally, it did not become routine practice for all the patients to receive CT scans until

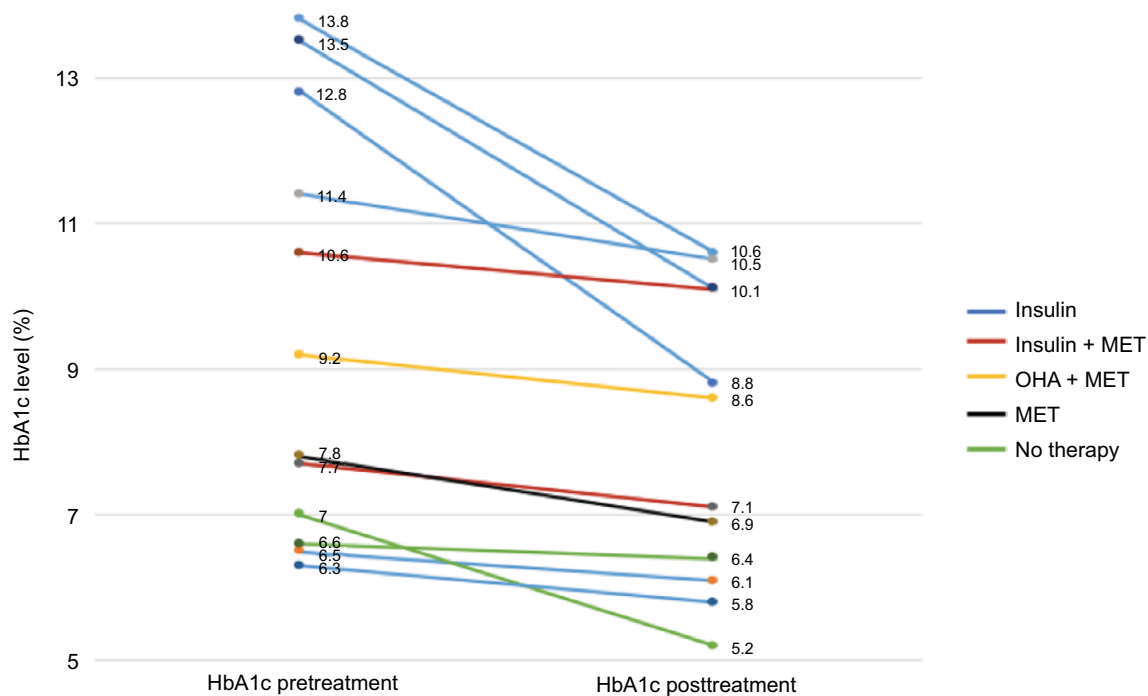


Figure 4 Patients with diabetes' HbA1c levels pre- and post-TB treatment.

Abbreviations: HbA1c, glycated hemoglobin; MET, metformin; OHA, oral hypoglycemic agents; TB, tuberculosis.

the later years of the study, limiting the comparison of all chest X-rays to CT imaging.

Given that the treatment of TB in patients with DM likely requires special considerations, our findings suggest that chest CT scan should be prospectively evaluated among other mechanisms to individualize therapy. For instance, in some settings, slow response to TB therapy has been attributed to suboptimal pharmacokinetics, which may be more important in the DM host with an already higher microbiological burden or uncoordinated immune response.^{25–27} The use of therapeutic drug monitoring early in the TB treatment course for patients with DM to dose adjust the first-line anti-TB drugs has in at least one programmatic setting been found to hasten the microbiological clearance of cultured *M. tuberculosis* from the sputum.^{28,29} Therefore, undertaking a prospective study of pharmacokinetics and dose adjustment of anti-TB medication in DM/TB compared to non-DM/TB may be particularly important for those patients with cavitory disease

Conclusion

The presence of lung cavities was significantly associated with the presence of DM and the level of HbA1c in pulmonary TB patients. CT scanning especially in those with normal radiography increases the frequency of detecting cavities. These findings may be important to determine the

optimal diagnostic approach in DM/TB endemic areas, such as Saudi Arabia, with access to CT scanners and whether such enhanced cavitory detection should signal an intensification or prolongation of TB or DM treatment.

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Disclosure

The authors report no conflicts of interest in this work.

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