Diabetes-related tuberculosis in the Middle East: an urgent need for regional research

Yosra M. Alkabab⁎, Hail M. Al-Abdely, and Scott K. Heysell

Division of Infectious Diseases, King Khalid University Hospital, Riyadh, Saudi Arabia
Division of Infectious Diseases, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia
Division of Infectious Diseases and International Health, University of Virginia, Charlottesville, Virginia, USA

Abstract

Objectives—Diabetes mellitus (DM) triples the risk of tuberculosis (TB) disease, complicates TB treatment, and increases the risk of a poor TB outcome. As DM prevalence is increasing across the Middle East, this review was performed to identify regional gaps in knowledge and research priorities for DM/TB.

Methods—Online databases were searched for studies published from Middle East countries on DM and TB and the studies summarized based on topic and major findings. Studies included had a principle hypothesis related to both diseases, or described TB patients with individual data on DM.

Results—Fifty-nine studies from 10 countries met search criteria. No published studies were found from Lebanon, Bahrain, Syria, Jordan, Cyprus, or the United Arab Emirates. DM prevalence among TB patients was high, but varied considerably across studies. The vast majority of studies were not specifically designed to compare DM/TB and non-DM/TB patients, but many suggested worse treatment outcomes for DM/TB, in accordance with reports from other regions.

Conclusions—Opportunity exists for the regional study of bidirectional screening, management strategies for both DM and TB diseases, and whether such efforts could take place through the integration of services.

Keywords
Tuberculosis; Diabetes mellitus; Middle East; Iran; Turkey; Saudi Arabia

1. Introduction

Diabetes mellitus (DM) is an increasingly recognized comorbidity that can both accelerate tuberculosis (TB) disease and complicate TB treatment. DM triples the risk of developing
active TB following infection compared to patients without DM. Indeed, in regions of the world with high DM prevalence, the risk of developing TB disease attributable to DM exceeds even that of HIV. Better understanding of the DM/TB dynamic led to the recent World Health Organization (WHO) Collaborative Framework for Care and Control of Tuberculosis and Diabetes, which emphasizes bidirectional screening to identify latent TB infection in patients with DM, or newly diagnose DM in patients with active TB. Such interventions may ultimately lead to increased dual detection in regions of high co-prevalence. Nevertheless, there are considerable gaps in knowledge with regard to strategies for implementation of bidirectional screening, as well as other more fundamental questions related to pathophysiology and immunology, clinical presentation, and treatment approach for both diseases in the DM/TB host.

Importantly, these interventions must be regionally distinct and will depend significantly on the local epidemiology and standards of care. The estimated number of prevalent TB cases in the WHO Eastern Mediterranean Region (the region of most overlap with the queried Middle East countries) has been reported to be 1,000,000 (880,000–1,200,000). Comparatively, the International Diabetes Foundation (IDF) has reported that in the Middle East and North Africa alone, 35 million people are living with DM. Figure 1 illustrates the top 10 countries for age-adjusted prevalence of DM, three of which are in the Middle East (Saudi Arabia, Kuwait, and Qatar). Yet despite this ecological association, and relative to the potential magnitude of the public health problem, DM/TB in the Middle East remains understudied. Therefore, a literature review was conducted to summarize the existing research related to DM/TB from the Middle East region, to highlight region-specific gaps in knowledge, and to prioritize areas for further investigation in the context of WHO recommendations.

2. Methods

While this study was not a meta-analysis, PRISMA guidelines were adhered to whenever possible. The PubMed and Google Scholar databases were searched using the following English-language terms: “tuberculosis” AND “diabetes” AND/OR “middle east” OR the following countries, “Iraq,” “Yemen,” “Kuwait,” “Iran,” “Bahrain,” “Egypt,” “Syria,” “Turkey,” “Lebanon,” “Oman,” “Qatar,” “Saudi Arabia,” “Israel,” “Jordan,” “UAE,” “Cyprus” OR “United Arabs Emirates.” As no consensus definition for ‘Middle East’ countries exists, the United Nations definition for Western Asia was employed, and Egypt and Turkey were also included. Reference sections of articles derived from the database search were also checked for additional studies. The initial database search was performed by one author (YMA), while two others (HMA and SKH) agreed on the final list for inclusion. All studies for which there was access to full-text and that had a principle hypothesis related to both diseases and/or any study of TB patients that reported individual data on DM, were included. Articles written in the English language were included and were grouped by major topic and country of origin. A priori topics of interest included regional DM/TB epidemiology, bidirectional screening, clinical manifestations, immunology, pharmacokinetics, and management strategies.
3. Results

Fifty-nine studies were found that met the search criteria, representing 10 separate countries. A total of 17 studies were case–control studies comparing DM/TB to non-DM/TB patients. Five studies were cross-sectional, one was prospective, and the remainder were retrospective studies evaluating the demographic and clinical characteristics of TB-infected patients. Iran contributed the most studies (16 studies) and the fewest were from Yemen and Oman (one each). Importantly, no published studies were found from Lebanon, Bahrain, Syria, Cyprus, Jordan, and the UAE. As only English-language articles were included, abstracts were then further searched in other regional languages (Arabic, Farsi, and Turkish), which revealed one study in Farsi from Iran that was then included.

Table 1 summarizes the studies grouped by topic, the important features of which are discussed in the following sections.

3.1. Epidemiology

Analysis of the WHO and IDF country-level surveillance data alongside that reported from the individual studies, demonstrated a considerable co-prevalence of DM/TB (Table 2). Yemen leads the region with regard to TB prevalence, and despite a comparatively low DM prevalence, 21% of all TB patients in one study were reported to have DM. The greatest numbers of studies of co-prevalence were from Saudi Arabia, Iran, and Turkey, with proportions varying from less than 10% to more than 30%.

3.2. Screening for TB in diabetic patients

Despite the apparent benefit of bidirectional screening in other settings, only one study from the Middle East was found that specifically addressed this topic. The study had a cross-sectional design and was conducted in a diabetes center in Iran; the principal aim was to identify the number of smear-positive pulmonary TB patients with DM. Four hundred patients with DM all received a tuberculin skin test (TST). The test result was negative (induration of 0–4 mm) in 257 patients (64.25%), intermediate (induration of 5–9 mm) in 118 patients (29.5%), and positive (induration of 10–14 mm) in 25 patients (6.25%). Twenty-four of the 400 (6%) were suspected to have TB by symptoms (cough >3 weeks, hemoptysis, and fever) and underwent testing of sputum for acid-fast bacilli (AFB) and a chest X-ray. Of the 24 suspected cases, four (one with an intermediate TST and three with a positive TST) had a positive sputum smear for AFB and the diagnosis of active TB was made. The rate of detection of active TB was considered greater than the expected community prevalence and the authors recommended continued screening in all patients with DM. No other study was found that addressed screening or treatment of latent TB infection in DM patients, or active screening for the presence or severity of DM in patients with known TB.

3.3. Immunology

Currently, it is understood that both the innate and adaptive immune response are important in preventing progression from TB infection to active disease, and DM may impair multiple aspects of the coordinated response. The bulk of studies found from the Middle East focused on the cell-mediated immune response in the DM/TB disease state. A study from

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Iraq showed a significant decrease in the concentration of the cytokines interferon gamma (IFN-γ) and interleukin 2 (IL-2) in DM/TB patients compared to non-diabetic TB patients. Additionally, a study from Iran demonstrated a statistically significant reduction in the total T-lymphocyte population, particularly the T-helper sub-class, in DM/TB patients compared with both non-diabetic TB patients and healthy controls. Furthermore, a study from Kuwait found DM/TB patients to have a lower Th1:Th2 cytokine ratio, leading to a stronger Th2 bias, and this has been hypothesized elsewhere to contribute to the faster clinical deterioration in DM/TB patients. Another study in Kuwait was conducted to evaluate cell-mediated responses to complex, single secreted, and cytosolic antigens of *Mycobacterium tuberculosis* and posited that only ESAT6 (6 kDa early secretory antigenic target) could be useful in the diagnosis of infection in both DM/TB and non-diabetic patients.

### 3.4. Clinical presentation of DM/TB

The variation in DM/TB clinical presentation compared to TB patients without DM has been commented on over many years, with a focus on demographics, symptoms, anatomical distribution, chest X-ray abnormalities, and the influence of DM severity and glycemic control. Four studies (three case–control and one cross-sectional) were found that reported that DM/TB patients were older than non-diabetic TB patients, with the mean age of DM/TB patients being 50 ± 10 years. Similar to other reports outside the region, the majority of studies showed no difference by sex, but two case–control studies, one from Saudi Arabia and the other from Egypt, found patients with DM/TB significantly more likely to be male. While the bulk of studies found no difference in the clinical presentation of DM/TB compared to non-diabetic TB, two isolated reports found that diabetics were more likely to present with hemoptysis.

Regarding the duration of DM prior to patient presentation with TB infection, a cross-sectional study from Iraq, which included 50 DM/TB patients, and another case–control study from Turkey specifically aimed at evaluating features of DM/TB, respectively reported that 56% and 40% of the DM/TB patients had had DM for at least 10 years. Similarly, studies outside of the Middle East have supported the theory of worse glycemic control as a marker of disease severity predisposing to an increased rate of active TB disease among diabetics. The aforementioned study from Iraq found glycated hemoglobin (HgbA1c) to be poorly controlled (>8%) in 48% of DM/TB patients.

No prospective studies were found that addressed how HgbA1c or another marker of DM disease control changed with successful TB treatment.

Pulmonary TB is the most common anatomical presentation in DM/TB infection, but it is unclear if patients with DM are more likely to present with an extrapulmonary focus compared to patients without DM. A few studies were found that addressed this comparatively, but a study from Saudi Arabia suggested that bone disease was more frequent in DM/TB compared to non-diabetic TB. Furthermore, two related cases reported from Turkey highlighted the presentation of spondylitis and bone disease in DM/TB patients.

There are conflicting data regarding the effect of DM on the sputum smear results at the time of diagnosis of active pulmonary TB infection. Studies from the Middle East offer no further clarity. A case–control study from Turkey of patients with sputum culture proven TB,
found that those with DM/TB were significantly more likely to present with a negative AFB sputum smear upon presentation compared to non-diabetic TB patients. In contrast, the two other case–control studies from Saudi Arabia and Egypt that had similarly found DM/TB patients more likely to be male, concluded that DM/TB patients were more likely to have positive AFB sputum smears upon presentation.

### 3.5. Radiological presentation

Similar to the conflicting data regarding clinical presentation in DM/TB and non-diabetic TB, radiological appearances have often been thought to be more atypical in DM/TB, but some reports have demonstrated no appreciable between-group differences. The same conflict was observed in the Middle East studies, where several showed clinical significance in atypical imaging findings (lower lobe/multiple lobe presentation and diffuse involvement), other studies showed an increase in more typical findings such as cavitary lesions in DM/TB-infected patients as compared to non-diabetic TB patients, and yet another five studies showed no difference.

### 3.6. Drug-resistant TB

In certain settings, drug-resistant TB is associated with prior anti-TB drug treatment or nosocomial exposure, which may be more common in some subgroups like HIV-infected patients. Multidrug-resistant (MDR)-TB is defined in the presence of resistance to isoniazid and rifampicin, the two most important first-line anti-TB drugs. This predisposes the patient to a significant increase in morbidity and mortality when compared to drug-susceptible TB. Whether DM presents any additional risk for the development or acquisition of MDR-TB remains controversial. Three case–control studies comparing DM/TB and non-diabetic TB patients from Iran, Saudi Arabia, and Turkey showed no significant association between DM and the risk of MDR-TB. Additionally, three studies assessed general risk factors for MDR-TB infection among cohorts with TB. A retrospective study from Israel covering the period from 2000 to 2005, described 132 MDR-TB patients, of whom 17 (12.9%) had DM. In a national TB referral hospital in Iran, 234 non-MDR pulmonary TB patients were compared to 48 MDR pulmonary TB patients and DM was found in 6.4% in the MDR-TB group versus 9% in the non-MDR-TB group, a non-significant difference. This was also shown in another cross-sectional study in Turkey (with a total of 116 sputum culture-positive TB patients), where univariate analysis showed no association between DM and MDR-TB.

### 3.7. Pharmacokinetics

Several studies outside the region have suggested that patients with DM/TB may be prone to suboptimal circulating anti-TB drug concentrations, particularly rifampicin. A decrease in overall peak or total exposure to a particular drug is dependent on numerous factors, including host genetics related to xenobiotic transport and metabolism, but may also be secondary to a decrease in gastric hydrochloric acid secretion, gut transit time, and weight or volume of distribution, which may all be more problematic in the DM/TB patient.
A single case–control study from Turkey addressed this topic. Fourteen DM/TB patients and 56 non-diabetic pulmonary TB patients were studied. The estimated peak plasma concentrations of isoniazid and rifampicin were approximately 50% lower in the DM/TB patients. All DM/TB patients had isoniazid and rifampicin concentrations that were below the expected range. Pyrazinamide and ethambutol concentrations were similar in both groups.47

3.8. Sputum conversion

Sputum conversion not only guides the duration of TB treatment and infectivity of the patient, but delayed conversion is also associated with an increased risk of relapse. While most studies outside of the Middle East have shown no relationship between DM and conversion at the end of 2 months,74,79 other studies have shown an overall increased time to sputum conversion,80,82 and in addition, DM/TB patients with HbA1c values ≥7 have been observed to have a greater risk of a persistently positive sputum culture at the end of 2 months.81 A relatively large retrospective review at a TB referral hospital in Turkey did not find a statistically significant difference in sputum culture conversion at the end of 2 months of treatment, but the duration of therapy was significantly longer in DM/TB patients.42 Furthermore, another study from a referral hospital in Turkey specifically addressed risk factors for delayed sputum conversion. Among 306 patients, of whom 14% had DM, DM/TB was significantly associated with a delay in the time to both smear and culture conversion.43 Another case–control study from Turkey supported these findings.44 Additionally, in a study from Saudi Arabia, DM was significantly associated with persistent sputum positivity after 2 months of treatment, but regression analysis found age and disease burden (number of bacilli in pretreatment sputum and cavitary lung disease) were the dominant predictors overall.57 Lastly, one study from Oman in which 112 pulmonary TB patients were treated for 2 months in the hospital before sputum for AFB smear was repeated (repeat TB culture was not performed), rates of smear conversion were similar for DM/TB and non-DM/TB patients.66

3.9. Overall treatment outcomes

In the aforementioned study from Turkey,42 DM/TB patients were more likely to require more than 6 months to achieve cure for pulmonary TB compared to non-diabetic TB patients. In a study from Egypt specifically carried out to study the risk factors for TB treatment failure,34 119 patients with treatment failure were matched to an equal number who had been successfully cured and the presence of DM increased the risk of failure by more than 9-fold, including among those with reported adherence under a directly observed TB treatment schedule. Another retrospective study done in a TB referral center in Iran included the medical records of 715 pulmonary TB patients seen over a 15-year span, of whom 75 had died during therapy.15 On multivariate analysis, DM was independently associated with mortality (adjusted odds ratio 9.6, 95% confidence interval 5.7–16.1, p < 0.001).23 Moreover, a study from Kuwait assessed the prevalence and risk factors for default from pulmonary TB treatment and found that DM/TB patients were at increased risk of default in the adjusted analysis compared to non-diabetic TB patients.39 Comparatively, four other less rigorous studies showed no association of DM and poor treatment outcome.55,61,67,68
4. Discussion

DM prevalence among patients with TB will continue to increase given the projected global expansion of DM, and many countries of the Middle East region appear particularly vulnerable. The studies summarized from the Middle East demonstrated high co-prevalence rates, with a prevalence of DM among TB patients ranging from approximately 5% to more than 40%. The vast majority of studies were retrospective analyses without a specific design to compare DM/TB and non-DM/TB patients, and while certain countries had numerous studies (Turkey, Iran, and Saudi Arabia), there were six countries for which studies of DM/TB were not found (Bahrain, Cyprus, Jordan, Lebanon, Syria, and UAE).

Despite the recommendation to screen for DM in patients with active TB, there were no studies that examined the best method or could comment on the diagnostic yield, even though in many referral hospitals in Middle Eastern countries such screening is practiced routinely. Furthermore, only one study examined the role of screening patients with DM for active TB and suggested this may be of clinical benefit. Yet the widespread adoption of such screening would certainly depend upon cost-effectiveness analyses, including the method of screening (symptoms, sputum diagnostics, and/or imaging) and local TB prevalence. Similarly, studies of screening and treatment for latent TB infection in patients with DM were not found. Hence, more comprehensive local studies of bidirectional screening appear urgently needed given the relative public health urgency of the DM/TB problem in the region.

The bulk of studies examined hospitalized patients with TB and either directly compared DM/TB patients and non-diabetic TB patients, or reported DM among numerous other clinical and demographic factors. Either very little difference or conflicting reports were noted with regard to the clinical presentation and radiographic findings in DM/TB compared to non-DM/TB. Yet these investigations appear of less research importance compared to the findings that patients with DM/TB may have a delay in microbiological response to treatment and an increased risk of death, which could be related to their disease burden at presentation, underlying immune dysregulation, impaired pharmacological exposure, or simply that DM may associate with other morbidities (e.g., renal dysfunction) that may not have been reported or adequately adjusted for in analyses. It was not possible to examine other potential confounders in the studies that reported on treatment outcome. For example, the common anti-diabetic drug, metformin, has recently been suggested to have direct anti-TB activity.

With the knowledge gaps identified in this review, there exists considerable potential for meaningful study of DM/TB in the region. In many TB-endemic countries, DM care is unavailable, poorly accessed, or restricted due to the poor supply and high costs of drugs or lack of specialists. In contrast, a comparatively high availability of DM care is present in many countries of the Middle East. Saudi Arabia, Bahrain, Oman, and Qatar were among the top 10 countries with the highest health expenditure for DM as measured by percentage of the national health expenditure in 2010. Therefore the integration of DM and TB services in these countries may be more feasible and cost-effective. Other target
areas for research should focus on understanding and optimizing DM/TB treatment outcomes, which may include study of intensified TB treatment regimens, therapeutic drug monitoring, optimal duration of TB therapy, or the use of adjunctive or immunomodulating agents.

In conclusion, a review of studies published from the Middle East found a relative lack of investigation specifically designed to assess differences in DM/TB compared to non-DM/TB. Future studies should account for DM disease severity and anti-diabetic treatment, as well as assure laboratory confirmed absence of hyperglycemia in subjects categorized as non-diabetic. Opportunity exists for the study of bidirectional screening, management strategies for both DM and TB diseases, and whether such efforts could take place through the integration of services.

References

1. Baker MA, Harries AD, Jeon CY, Hart JE, Kapur A, Lönnroth K, et al. The impact of diabetes on tuberculosis treatment outcomes: a systematic review. BMC Med. 2011; 9:81. [PubMed: 21722362]
2. Dye C, Trunz B, Lönnroth K, Roglic G, Williams B. Nutrition, diabetes and tuberculosis in the epidemiological transition. PLoS One. 2011; 6:e21161. [http://dx.doi.org/10.1371/journal.pone.0021161]. [PubMed: 21712992]
3. Ruslami R, Aarnoutse RE, Alisjahbana B, van der Ven AJ, van Crevel R. Implications of the global increase of diabetes for tuberculosis control and patient care. Trop Med Int Health. 2010; 15:1289–99. [PubMed: 20954995]
4. Collaborative framework for care and control of tuberculosis and diabetes: report by WHO and IUATLD. World Health Organization; Geneva: 2011. Available at: [http://whqlibdoc.who.int/publications/2011/9789241502252_eng.pdf] [accessed 9 November 2014]
5. Jeon CY, et al. Bi-directional screening for tuberculosis and diabetes: a systematic review. Trop Med Int Health. 2010; 15:1300–14. [PubMed: 20958887]
6. World Health Organization. Global tuberculosis control 2014. WHO; Geneva, Switzerland: 2014. WHO/HTM/TB/2014.7
7. International Diabetes Federation. IDF diabetes atlas. 6th ed. International Diabetes Federation; Brussels, Belgium: 2013. Available at: [http://www.idf.org/diabetesatlas] [accessed 9 November 2014]
8. Moher D, Liberati A, Tetzlaff J, Altman DG, the PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009; 6:e1000097. [http://dx.doi.org/10.1371/journal.pmed.1000097]. [PubMed: 19621072]
9. [accessed 28 June 2015] List of country groupings and sub-groupings for the analytical studies of the United Nations World Economic Survey and other UN reports. Mar 3. 2008 Available at: [http://unpan1.un.org/intradoc/groups/public/documents/un/unpan008092.pdf]
10. Anaam M, Ibrahim M, Serouri A, Bassili A, Aldobhani A. A nested case–control study on relapse predictors among tuberculosis patients treated in Yemen’s NTCP. Public Health Action. 2012; 2:168173.
11. Ibrahim WH, et al. Does pleural tuberculosis disease pattern differ among developed and developing countries. Respir Med. 2005; 99:1038–45. [PubMed: 15950146]
12. Khan FY, Al-Muzrakchi AM, Elbedawi MM, Al-Muzrakchi AA, Al Tabeb A. Peritoneal tuberculosis in Qatar: a five-year hospital-based study from 2005 to 2009. Travel Med Infect Dis. 2012; 10:25–31. [PubMed: 22209118]
13. Al Marri MR. The tuberculin skin test in confirmed pulmonary tuberculosis in the state of Qatar: where we stand? Qatar Med J. 2013; 2012(2):16–9. [PubMed: 25003035]
14. Kermansaravi F, Metanat M, Shariﬁ-Mood B. Evaluation of active pulmonary tuberculosis among patients with diabetes. Int J Infect. 2014; 1:e19632.

Int J Infect Dis. Author manuscript; available in PMC 2016 May 11.
15. Alavi SM, Salami S. The causes of death among patients with tuberculosis in Khuzestan, Iran. Pak J Med Sci. 2008; 24:217–20.

16. Baghaei P, Tabarsi P, Abrishami Z, Mirsaedi M. Comparison of pulmonary TB patients with and without diabetes mellitus type II. Tanaffos. 2010; 9:13–20.

17. Alavi SM, Sharifi M. Tuberculous spondylitis: risk factors and clinical/para-clinical aspects in the south west of Iran. J Infect Public Health. 2010; 3:196–200. [PubMed: 21126725]

18. Towhidi M, Azarian A, Asnaashari A. Pulmonary tuberculosis in the elderly. Tanaffos. 2008; 7:52–7.

19. Mansoori D, Jamaati H, Arami S, Zadsar M. Comparison of lymphocyte number and their subsets in patients with diabetes mellitus type II, tuberculosis and concomitant TB and diabetes. Tanaffos. 2002; 1:45–50.

20. Metanat M, Sharifi-Mood B, Rohani Z, Namroodi B. Hospitalization among diabetic adults due to infectious diseases in Zahedan. Iranian Journal of Clinical Infectious Diseases. 2008; 3:89–92.

21. Alavi SM, Ahmadi F, Zargari N. The main risk factors of pulmonary tuberculosis acquisition in hospitalized patients in Razi Hospital, Ahvaz-Iran (2001–07). J Gorgan Uni Med Sci. 2012; 14:106–11.

22. Jamzad A, Shahnazi M, Khatami A, Azimi G. Radiographic findings of pulmonary tuberculosis in Tehran in comparison with other institutional studies. Iran J Radiol. 2009; 6:131–6.

23. Alavi-Naini R, Moghtaderi A, Metanat M. Factors associated with mortality in tuberculosis patients. J Res Med Sci. 2013; 18:52–5. [PubMed: 23901338]

24. Baghaei P, Marjani M, Moniri A. Screening of diabetes mellitus among new cases of tuberculosis. Eur Respir J. 2013; 42:2774.

25. Alavi SM, Khoshkhoy MM. Pulmonary tuberculosis and diabetes mellitus: coexistence of both diseases in patients admitted in a teaching hospital in the southwest of Iran. Caspian J Intern Med. 2012; 3:421–4. [PubMed: 24358437]

26. Heidarnedjad H, Bahrami A. Lower lung field tuberculosis: an analysis of 146 cases. MJIRI. 1991; 3–4:111–6.

27. Baghaei P, Tabarsi P, Chitsaz E, Novin A. Risk factors associated with multidrug-resistant tuberculosis. Tanaffos. 2009; 8:17–21.

28. Al-Saadi M, Al-Khafaji J, Sheriff NA. Effect of cytomegalovirus and diabetes mellitus on the cytokine profile of cellular immunity in tuberculosis patients. Br J Med Res. 2014; 4:883–8.

29. Khalil I. The relationship between tuberculosis and diabetes mellitus in patients. Al-Kufa Journal for Biology. 2011; 3:185–92.

30. El-Hini S, Farghaly E, Osmanet A. Relation between type 2 diabetes mellitus and pulmonary tuberculosis: clinical implication and insulin sensitivity. El-minia Medical Bulletin. 2007; 18:157–70.

31. Rabie G, Farghly E, El Hosseiny M, Ali A, El-Hini E. Risk factors of pulmonary tuberculosis in upper Egypt. El-minia Medical Bulletin. 2008; 19:181–98.

32. El-Warraki S. The pattern and behavior of 582 pulmonary tuberculosis in diabetic patients. Dis Chest. 1963; 43:582–6. [PubMed: 13993650]

33. Abdelmoez B, Abd-El-Nasser A, Baheeg M, Sedky A. Prevalence of tuberculosis among children who had type 1 diabetes and were admitted to Elminia University Hospital. Pediatrics. 2008; 121:S151.

34. Morsy A, Zaher H, Hassan M. Predictors of treatment failure among tuberculosis patients under DOTS strategy in Egypt. East Mediterr Health J. 2003; 9:689–701. [PubMed: 15748066]

35. Ali O, Mahalli E. Drug resistant tuberculosis: risk factors and resources-utilization at a chest disease clinic, Alexandria, Egypt. J Am Sci. 2012; 8:16–22.

36. Al-Attiyah R, Mustafa A. Mycobacterial antigen-induced T helper type 1 (Th1) and Th2 reactivity of peripheral blood mononuclear cells from diabetic and non-diabetic tuberculosis patients and Mycobacterium bovis bacilli Calmette–Guérin (BCG)-vaccinated healthy subjects. Clin Exp Immunol. 2009; 158:64–73. [PubMed: 19737232]
37. Mustafa AS, El-Shamy AM, Madi NM, Amoudy HA, Al-Attiyah R. Cell-mediated immune responses to complex and single mycobacterial antigens in tuberculosis patients with diabetes. Med Princ Pract. 2008; 17:325–30. [PubMed: 18523402]
38. Shamy E, Saidi A, Baidas G. Military tuberculosis in Kuwait: clinical presentation, diagnosis and treatment outcome. Kuwait Med J. 2008; 40:288–92.
39. Zhang Q, Gaffer M, Bayoumy M. Determinants of default from pulmonary tuberculosis treatment in Kuwait. Sci World J. 2014; 2014:672825.
40. Abal AT, et al. Demographic pattern and clinical characteristics of patients with smear-positive pulmonary tuberculosis in Kuwait. Med Princ Pract. 2005; 14:306–12. [PubMed: 16103695]
41. Surucuoglu S, et al. Drug-resistant pulmonary tuberculosis in western Turkey: prevalence, clinical characteristics and treatment outcome. Ann Saudi Med. 2005; 25:313–8. [PubMed: 16212125]
42. Tatar D, et al. Tuberculosis in diabetics: features in an endemic area. Jpn J Infect Dis. 2009; 62:423–7. [PubMed: 19934532]
43. Güler M, Unsal E, Dursun B, Aydın O, Capan N. Factors influencing sputum smear and culture conversion time among patients with new case pulmonary tuberculosis. Int J Clin Pract. 2007; 61:231–5. [PubMed: 17166185]
44. Yurteri G, et al. Features of pulmonary tuberculosis in patients with diabetes mellitus: a comparative study. Turkish Respiratory Journal. 2004; 5:5–8.
45. Akguns M, Kaynar H, Saglam L, Araz O, Ozden K. Clinical and social characteristics of the patients with tuberculosis in Eastern Anatolia. Tüberkülöz ve Toraks Dergisi. 2006; 54:349–54.
46. Abakay O. Clinical and laboratory characteristics of 48 patients with miliary tuberculosis. Afr J Microbiol Res. Dec 9; 2011 5(29):5292–6.
47. Babalik A, et al. Plasma concentrations of isoniazid and rifampin are decreased in adult pulmonary tuberculosis patients with diabetes mellitus. Antimicrob Agents Chemother. 2013; 57:5740–2. [PubMed: 23979746]
48. Elmas Ö, Akıncı A, Bilir P. Tuberculous meningitis associated with diabetic ketoacidosis. J Clin Res Pediatr Endocrinol. 2011; 3:222–4. [PubMed: 22155468]
49. Yasar K, Pehlivanoğlu F, Sengöz A, Sengoğ G. Coexistence of advanced age and female gender in diabetics with extrapulmonary tuberculosis: four culture-proven cases. Gender Medicine. 2011; 8:334–8. [PubMed: 21689993]
50. Ocal S, Saka D, Oğretensoy M. Mild and severe forms of tuberculosis in diabetic and non-diabetic patients. J Diabetes. 2009; 1:107–11. [PubMed: 20929507]
51. Bacakoğlu F, Başoğlu OK, Cok G, Sayiner A, Ateş MM. Pulmonary tuberculosis in patients with diabetes mellitus. Respiration. 2001; 68:595–600. [PubMed: 11786714]
52. Tanrikulu AC, Hosoglu S, Ozbekici T, Abakay A, Gurkan F. Risk factors for drug resistant tuberculosis in southeast Turkey. Trop Doct. 2008; 38:91–3. [PubMed: 18453496]
53. Al-Tawfiq JA, Saadeh BM. Radiographic manifestations of culture-positive pulmonary tuberculosis: cavitary or non-cavitary? Int J Tuberc Lung Dis. 2009; 13:367–70. [PubMed: 19275798]
54. Shaikh MA, Singla R, Khan NB, Sharif NS, Saigh MO. Does diabetes alter the radiological presentation of pulmonary tuberculosis. Saudi Med J. 2003; 24:278–81. [PubMed: 12704504]
55. Singla R, et al. Influence of diabetes on manifestations and treatment outcome of pulmonary TB patients. Int J Tuberc Lung Dis. 2006; 10:74–9. [PubMed: 16466041]
56. Al-Jahdali H, et al. Clinical aspects of miliary tuberculosis in Saudi adults. Int J Tuberc Lung Dis. 2000; 4:252–5. [PubMed: 10751072]
57. Singla R, et al. Factors predicting persistent sputum smear positivity among pulmonary tuberculosis patients 2 months after treatment. Int J Tuberc Lung Dis. 2003; 7:58–64. [PubMed: 12701836]
58. Bukhary ZA, Alrajhi AA. Extrapulmonary tuberculosis, clinical presentation and outcome. Saudi Med J. 2004; 25:881–5. [PubMed: 15235693]
59. Al-Hajjaj MS. The outcome of tuberculosis treatment after implementation of the national tuberculosis control program in Saudi Arabia. Ann Saudi Med. 2000; 20:125–8. [PubMed: 17322708]
60. Hakawi A, Alrajhi A. Tuberculosis of the bone marrow: clinico-pathological study of 22 cases from Saudi Arabia. Int J Tuberc Lung Dis. 2006; 10:1041–4. [PubMed: 16964798]

61. Siddiqui A. Clinical manifestations and outcome of tuberculosis in diabetic patients admitted to King Abdulaziz University Hospital in Jeddah, Saudi Arabia. Journal of Taibah University Medical Sciences. 2009; 4:148–54.

62. Singla R, Al-Sharif N, Al-Sayegh M, Osman M. Prevalence of resistance to anti-tuberculosis drugs in Riyadh and a review of previous reports. Ann Saudi Med. 2003; 23:143–7. [PubMed: 16985303]

63. Alzohairy MA. Epidemiology of tuberculosis among migrant workers in Qassim Area, Saudi Arabia. Research Journal of Medical Sciences. 2011; 5:233–6.

64. Samman Y, et al. Clinical pattern of tuberculosis among Saudi nationals in the western region of Saudi Arabia. Tanaffos. 2005; 4:37–42.

65. Al-Wabel AH, Teklu B, Mahfouz A. Symptomatology and chest roentgenographic changes of pulmonary tuberculosis among diabetics. East Afr Med J. 1997; 74:62–4. [PubMed: 9185385]

66. Pajankar S, Khandekar R, Amri AM. Factors influencing sputum smear conversion at one and two months of tuberculosis treatment. Oman Medical Journal. 2008; 23:263–8. [PubMed: 22334839]

67. Bendayan D, Hendler A, Polansky V, Weinerberger M. Outcome of hospitalized MDR-TB patients: Israel 2000–2005. Eur J Clin Microbiol Infect Dis. 2010; 30:375–9. [PubMed: 20972692]

68. Lubart E, Lidi M, Leibovitz A. Mortality of patients hospitalized for active tuberculosis in Israel. IMAJ. 2007; 9:870–3. [PubMed: 18210928]

69. Jeon C, Murray M. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. PLoS Med. 2008; 5:e152. http://dx.doi.org/10.1371/journal.pmed.0050152. [PubMed: 18630984]

70. Dooley KE, Chaisson RE. Tuberculosis and diabetes mellitus: convergence of two epidemics. Lancet Infect Dis. 2009; 9:737–46. [PubMed: 19926034]

71. Wang CS, Yang CJ, Chen HC. Impact of type 2 diabetes on manifestations and treatment outcome of pulmonary tuberculosis. Epidemiol Infect. 2009; 137:203–10. [PubMed: 18559125]

72. Riza AL, Pearson F, Ugarte-Gil C, Alisjahbana B. Clinical management of concurrent diabetes and tuberculosis and the implications for patient services. Lancet Diabetes Endocrinol. 2014; 2:740–53. [PubMed: 25194887]

73. Webb EA, Hesseling AC, Schaaf HS. High prevalence of Mycobacterium tuberculosis infection and disease in children and adolescents with type 1 diabetes mellitus. Int J Tuberc Lung Dis. 2009; 13:868–74. [PubMed: 19555537]

74. Alisjahbana B, Sahiratmadja E. The effect of type 2 diabetes mellitus on the presentation and treatment response of pulmonary tuberculosis. Clin Infect Dis. 2007; 45:428–35. [PubMed: 17638189]

75. Wang JY, Lee LN, Hsueh PR. Factors changing the manifestation of pulmonary tuberculosis. Int J Tuberc Lung Dis. 2005; 9:777–83. [PubMed: 16013774]

76. Harries A, et al. The looming epidemic of diabetes-associated tuberculosis: learning lessons from HIV-associated tuberculosis. Int J Tuberc Lung Dis. 2011; 15:1436–44. [PubMed: 21902876]

77. Nissapatorn V, Kuppusamy I, Jamaih I. Tuberculosis in diabetic patients: a clinical perspective. Southeast Asian J Trop Med Public Health. 2005; 36:213–20. [PubMed: 16438212]

78. Shenoi S, Heysell S, Moll A. Multidrug-resistant and extensively drug-resistant tuberculosis: consequences for the global HIV community. Curr Opin Infect Dis. 2009; 22:11–7. [PubMed: 19532076]

79. Kameda K, Kawabata S, Masuda N. Follow-up study of short course chemo-therapy of pulmonary tuberculosis complicated with diabetes mellitus. Kekkaku. 1990; 65:791–803. [PubMed: 2077255]

80. Chang JT, Dou HY, Yen CL, Wu YH, Huang RM, Lin HJ, et al. Effect of type 2 diabetes mellitus on the clinical severity and treatment outcome in patients with pulmonary tuberculosis: a potential role in the emergence of multidrug resistance. J Formos Med Assoc. 2011; 110:372–81. [PubMed: 21741005]

81. Park SW, Shin JW, Kim JY, Park IW, Choi BW, Choi JC, et al. The effect of diabetic control status on the clinical features of pulmonary tuberculosis. Eur J Clin Microbiol Infect Dis. 2012; 31:1305–10. [PubMed: 22042559]
82. Heysell SK, Moore JL, Keller SJ, Houpt ER. Therapeutic drug monitoring for slow response to tuberculosis treatment in a state control program, Virginia, USA. Emerg Infect Dis. 2010; 16:1546–53. [PubMed: 20875279]

83. Gwilt PR, Nahhas RR, Tracewell WG. The effects of diabetes mellitus on pharmacokinetics and pharmacodynamics in humans. Clin Pharmacokinet. 1991; 20:477–90. [PubMed: 2044331]

84. Bashar M, Alcabes P, Rom WN, Condos R. Increased incidence of multidrug-resistant tuberculosis in diabetic patients on the Bellevue Chest Service, 1987 to 1997. Chest. 2001; 120:1514–9. [PubMed: 11713128]

85. Dostalek M, Akhlaghi F, Puzanovova M. Effect of diabetes mellitus on pharmacokinetic and pharmacodynamic properties of drugs. Clin Pharmacokinet. 2012; 51:481–99. [PubMed: 22668340]

86. Dooley KE, Tang T, Golub JE, Dorman SE, Cronin W. Impact of diabetes mellitus on treatment outcomes of patients with active tuberculosis. Am J Trop Med Hyg. 2009; 80:634–9. [PubMed: 19346391]

87. Van Crevel R, Dockrell HM, for the TANDEM Consortium. TANDEM: understanding diabetes and tuberculosis. Lancet Diabetes Endocrinol. 2014; 2:270–2. [PubMed: 24703039]

88. Heysell SK, Moore JL, Staley D, Dodge D, Houpt ER. Early therapeutic drug monitoring for isoniazid and rifampin among diabetics with newly diagnosed tuberculosis in Virginia. U.S.A. Tuberc Res Treat. 2013; 2013:6. Article ID 129723.

89. Grant P. Management of diabetes in resource-poor settings. Clin Med. 2013; 13:27–31.

90. Mendis S, et al. The availability and affordability of selected essential medicines for chronic diseases in six low-and middle-income countries. Bull World Health Organ. 2007; 85:279–88. [PubMed: 17546309]

91. Marais BJ, et al. Tuberculosis comorbidity with communicable and non-communicable diseases: integrating health services and control efforts. Lancet Infect Dis. 2013; 13:436–48. [PubMed: 23531392]

92. Zhang A, et al. Global healthcare expenditure on diabetes for 2010 and 2030. Diabetes Res Clin Pract. 2010; 87:293–301. [PubMed: 20171754]

93. Singhal A, et al. Metformin as adjunct antituberculosis therapy. Sci Transl Med. 2014; 6:263ra159.
Figure 1.
Of the top 10 countries with the highest age-adjusted prevalence of diabetes, three are in the Middle East. (Figure based on data from the International Diabetes Federation.\(^6\))
Table 1
Topic summaries of studies reviewed from the Middle East

| Topic                                      | Studies and summary of findings                                                                                                                                 |
|--------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Epidemiology of DM/TB                      | DM prevalence among TB patients ranged from 4% to 41%[10–13,15,17,18,21,26–28,30,31,34,35,38,40,41,43,45,60,52–54,66–68]                                                                          |
| TB screening among patients with DM        | Only one study from Iran screened for active TB among patients with DM and found four cases in 400 patients, a rate above the expected community prevalence[14]                                        |
| Immunology                                 | Four studies, two from Kuwait[36,37] and one each from Iraq[28] and Iran,[19] described cell-mediated immune dysregulation in DM/TB patients |
| Clinical presentation                      | The majority of studies found little difference in DM/TB patients and non-diabetic TB patients, although in some studies patients with DM were older; studies conflicted with regard to sex differences or sputum smear status. In total, 10 studies addressed this topic: five from Turkey,[42,48,49,51,52] two from Saudi Arabia,[53,54] one from Egypt,[30] one from Iraq,[28] and one from Iran[16] |
| Radiology                                  | Chest X-ray findings were highly variable and data were conflicting: studies reported more atypical presentation in DM/TB compared to non-DMTB, others less, and still others reported no difference between the groups. In total, 10 studies addressed this topic: three from Turkey,[42,44,51] three from Saudi Arabia,[53,54,65] two from Iran,[5,26] one from Egypt,[30] and one from Iraq[29] |
| Association with Mycobacterium tuberculosis drug resistance | Five studies commented on drug resistance, but none found DM to be an independent risk factor for MDR-TB: two from Iran,[16,27] and one each from Saudi Arabia,[55] Turkey,[62] and Israel[67] |
| Pharmacokinetics                           | A single study from Turkey found significantly reduced rifampicin and isoniazid exposure in DM/TB[47]                                                                                         |
| Sputum conversion                          | Five studies assessed risk factors for sputum smear and/or culture conversion after starting TB treatment and favored DM delaying a microbiological response to therapy: three studies from Turkey,[42–44] and one each from Oman[66] and Saudi Arabia[57] |
| Treatment outcome                          | While some studies showed no difference in TB treatment outcomes in patients with and without DM,[29,39,55,61,67,68] others found that DM prolonged treatment duration,[42] and increased the risk of treatment failure,[34] mortality,[15,23] and default.[39] In total, 10 studies addressed this topic: two from Iran,[15,23] two from Israel,[67,68] two from Saudi Arabia,[53,61] one from Turkey,[42] one from Egypt,[34] one from Kuwait,[39] and one from Iraq[29] |

DM, diabetes mellitus; TB, tuberculosis; MDR, multidrug-resistant.
Table 2
Diabetes mellitus and tuberculosis epidemiology and country-specific citations

| Country     | TB prevalence as the rate per 100 000 population (range) | DM prevalence as a percentage of the total population aged 20–79 years | Percentage range of DM prevalence among TB patients from studies included in this review | Range of study time periods | Mean age ± SD (years) of the study population |
|-------------|-----------------------------------------------------------|-------------------------------------------------|--------------------------------------------------|-----------------------------|---------------------------------------------|
| Yemen       | 60 (24–112)                                               | 8.45%                                           | 21%                                              | 2007–2010                   | <45 (89%)  ≥45 (11%)                        |
| Qatar       | 37 (11–79)                                                | 22.87%                                          | 5–25.5%                                          | 1996–2009                   | 34 ± 4                                      |
| Iran        | 32 (16–53)                                                | 9.9%                                            | 4.2–30%                                          | 1991–2008                   | 44 ± 5                                      |
| Iraq        | 29 (8.6–61)                                               | 9.5%                                            | 41.1%                                            | 2012–2013                   | 52 ± 10                                     |
| Egypt       | 27 (14–44)                                                | 16.8%                                           | 16.4–29.3%                                      | 2001–2011                   | 47 ± 6                                      |
| Kuwait      | 25 (7.3–52)                                               | 23.1%                                           | 29.8–35%                                        | 1996–2005                   | 37 ± 6                                      |
| Turkey      | 23 (11–39)                                                | 14.85%                                          | 7.9–34%                                          | 1997–2010                   | 41 ± 4                                      |
| Lebanon     | 16 (4.8–34)                                               | 15.0%                                           | No published studies                             |                             |                                             |
| Bahrain     | 15 (4.4–31)                                               | 21.8%                                           | No published studies                             |                             |                                             |
| Saudi Arabia| 14 (4.3–30)                                               | 23.87%                                          | 14–26%                                          | 1989–2009                   | 47 ± 13                                     |
| Syria       | 14 (4.2–30)                                               | 8.91%                                           | No published studies                             |                             |                                             |
| Oman        | 13 (4.7–25)                                               | 14.24%                                          | 25%                                              | 2001–2006                   | <20 (25%)  21–40 (37.5%)  41–60 (30.4%)  ≥61 (7.1%) |
| Israel      | 7.1 (2.9–13)                                              | 9.1%                                            | 5–12.9%                                          | 2000–2005                   | 50 ± 10                                     |
| Cyprus      | 6.6 (2.2–13)                                              | 9.3%                                            | No published studies                             |                             |                                             |
| Jordan      | 5 (1.5–10)                                                | 11.4%                                           | No published studies                             |                             |                                             |
| UAE         | 1.3 (0.38–2.7)                                            | 18.98%                                          | No published studies                             |                             |                                             |

TB, tuberculosis; DM, diabetes mellitus; SD, standard deviation; UAE, United Arab Emirates.

*Where there is only one study per country, the range (Iraq) or age category (Yemen and Oman) is given, as reported in the published articles.*