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

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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.[1] DM triples the risk of developing

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active TB following infection compared to patients without DM.[2] Indeed, in regions of the world with high DM prevalence, the risk of developing TB disease attributable to DM exceeds even that of HIV.[3] 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,[4] which emphasizes bidirectional screening to identify latent TB infection in patients with DM, or newly diagnose DM in patients with active TB.[5] 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).[7] 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.[8] 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.[9] 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.[10–68] A total of 17 studies were case–control studies comparing DM/TB to non-DM/TB patients.[16,19,25,28,30,36,37,42,44,47–51,54,55,65] Five studies were cross-sectional,[14,20,29,33,52] one was prospective,[10] 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.[21] 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,[5] 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.[14] 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.[69–71] 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

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.[28] 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.[19] 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.[36] 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.[37]

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.[70,72] 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.[29,42,50,54] Similar to other reports outside the region, the majority of studies showed no difference by sex,[38,43,50,52] but two case–control studies, one from Saudi Arabia[54] and the other from Egypt,[30] 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,[29,42,48–51,54,60] two isolated reports found that diabetics were more likely to present with hemoptysis.[16,30]

Regarding the duration of DM prior to patient presentation with TB infection, a cross-sectional study from Iraq,[29] which included 50 DM/TB patients, and another case–control study from Turkey specifically aimed at evaluating features of DM/TB,[42] 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.[73–75] The aforementioned study from Iraq found glycated hemoglobin (HgbA1c) to be poorly controlled (>8%) in 48% of DM/TB patients.[29] 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.[3] 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.[61] Furthermore, two related cases reported from Turkey highlighted the presentation of spondylitis and bone disease in DM/TB patients.[50]

There are conflicting data regarding the effect of DM on the sputum smear results at the time of diagnosis of active pulmonary TB infection.[70,72,76] 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.[51] In contrast, the two other case–control studies from Saudi Arabia[52] and Egypt[30] 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.[3,70,71,77] 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),[51,54] 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,[29,30,42,52] and yet another five studies showed no difference.[16,26,44,53,65]

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.[78] 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.[6] Whether DM presents any additional risk for the development or acquisition of MDR-TB remains controversial.[79–81] 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.[16,42,55] 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.[67] 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.[27] 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.[52]

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.[82,83] 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,[83] gut transit time,[84] and weight or volume of distribution, which may all be more problematic in the DM/TB patient.[85,86]

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,[72] 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,[4] 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,[16,19,25,28,30,36,37,42,44,47–51,54,55,65] 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[16,28,30,42,48,49,51,52,55,61] and radiographic findings[16,26,29,30,42,44,51,53,54,65] 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[43,44,57] and an increased risk of death,[15,23] which could be related to their disease burden at presentation, underlying immune dysregulation,[19,28,36,37] impaired pharmacological exposure,[47] 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.[93]

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.[89–91] 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.[92] Therefore the integration of DM and TB services in these countries may be more feasible and cost-effective.[6,71,72,92] Other target

areas for research should focus on understanding and optimizing DM/TB treatment outcomes[87], which may include study of intensified TB treatment regimens, therapeutic drug monitoring,[88] 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.

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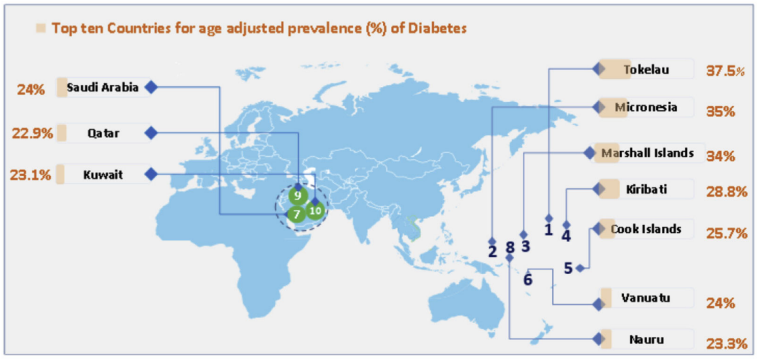

Figure 1.

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%[10–13,15,17,18,21,26–28,30,31,34,35,38,40,41,43,45,46,52–54,56–64,66–68]
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,[55,61] 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,[6,26] 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,[42] 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,[55,61] 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)[6]	DM prevalence as a percentage of the total population aged 20–79 years[7]	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[a]
Yemen	60 (24–112)	8.45%	21% [10]	2007–2010	<45 (89%) ≥45 (11%)
Qatar	37 (11–79)	22.87%	5–25.5% [11–13]	1996–2009	34 ± 4
Iran	32 (16–53)	9.9%	4.2–30% [15,17,18,21,26,27]	1991–2008	44 ± 5
Iraq	29 (8.6–61)	9.5%	41.1% 28	2012–2013	52 ± 10
Egypt	27 (14–44)	16.8%	16.4–29.3% [30,31,34,35]	2001–2011	47 ± 6
Kuwait	25 (7.3–52)	23.1%	29.8–35% [38,40]	1996–2005	37 ± 6
Turkey	23 (11–39)	14.85%	7.9–34% [41,43,45,46,52]	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% [53,54,56–64]	1989–2009	47 ± 13
Syria	14 (4.2–30)	8.91%	No published studies		
Oman	13 (4.7–25)	14.24%	25% [66]	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% [67,68]	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.

[a]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.