CHEST

Defining a Research Agenda to Address the Converging Epidemics of Tuberculosis and Diabetes

Part 1: Epidemiology and Clinical Management

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There is growing interest in the interaction between type 2 diabetes mellitus (DM) and TB, but many research questions remain unanswered. Epidemiologists, basic scientists, and clinical experts recently convened and identified priorities. This is the first of two reviews on this topic, summarizing priority areas of research regarding epidemiology, clinical management, and public health. First, from an epidemiologic point of view, more study is needed to determine the importance of transient hyperglycemia in patients with TB and on the importance of DM for the global epidemic of multidrug resistant (MDR)-TB. Second, regarding the screening and clinical management of combined TB and DM (TB-DM), clinical trials and large cohort studies should examine the benefits of improved DM care as well as prolonged or intensified TB treatment on the outcome of TB-DM and investigate the cost-effectiveness of screening methods for DM among patients newly diagnosed with TB. Third, from a public health and health systems point of view, the population health impact and cost-effectiveness of different interventions to prevent or treat DM and TB in high-burden populations should be examined, and health-system interventions should be developed for routine TB-DM screening, management of DM after completion of TB treatment, and better access to DM services worldwide. Studies are needed across different ethnicities and settings given the heterogeneity of metabolic perturbations, inflammatory responses, medications, and access to health care. Finally, studies should address interactions between TB, DM, and HIV because of the convergence of epidemics in sub-Saharan Africa and some other parts of the world. CHEST 2017; 152(1):165-173

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ABBREVIATIONS: ART = antiretroviral therapy; DM = diabetes mellitus; HbA1c = glycated hemoglobin; LTBI = latent TB infection; MDR = multidrug resistant; NCD = noncommunicable disease; OGTT = oral glucose tolerance test

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The prevalence of type 2 diabetes mellitus (DM) continues to increase rapidly in low- and middle-income countries as a result of rapid urbanization[1] and nutrition transition,[2] combined with a genetic and epigenetic "mismatch" of their inhabitants with more affluent environments.[3] Already, about 80% of the 415 million estimated DM cases globally are in low- and middle-income countries. Diabetes increases the risk of many infectious diseases, including TB,[4] and the prevalence of DM is projected to rise most steeply in regions with a high TB incidence, such as Sub-Saharan Africa, over the next 30 years.[5] A high proportion of diabetes in low- and middle-income countries is undiagnosed, and diabetes screening can be more challenging during TB treatment due to stress hyperglycemia that might be transient.[6] Optimal TB treatment regimens for patients with diabetes have not been established, and many issues related to DM management during TB treatment remain unresolved. The scale of the health systems challenges regarding the interacting epidemics of TB and DM has yet to be fully realized. To address some of these issues, a group of international TB and DM experts convened at the National Institutes of Health (NIH) in May 2016 to discuss the convergent epidemics of these communicable and noncommunicable diseases regarding their epidemiology, underlying biological mechanisms, and clinical management. This review provides an overview of the topics discussed, ending with a list of research priorities, focusing on the epidemiology, public health, and clinical aspects of the TB-DM interaction.

Epidemiology and Public Health

Summary Points

- **DM increases risks of TB and poor TB treatment outcomes.**
- **There is a relationship between dysglycemia and TB risk.**
- **Improved nutrition (and higher BMI) is protective against TB; hence at a population level, the interplay between rising obesity and TB is unclear. At an individual level, higher BMI (without DM) may be protective, but the development of diabetes impairs immunity to TB.**
- **Prevalence of DM and metabolic syndrome in patients with HIV appears to be high, particularly among those receiving antiretroviral therapy (ART).**
- **The interactions among DM, HIV, and TB are multidimensional and poorly understood, limiting our ability to estimate future trends for these concurrent epidemics.**

Direction and Magnitude of TB and DM Associations

The adverse effects of DM on TB incidence and outcomes are now widely accepted. Systematic reviews have suggested a more than threefold increased risk of TB among patients with DM[7] and a doubling of prolonged sputum positivity, TB treatment failure, death, and relapse.[8] However, it is important to note that the increased TB risk in patients with DM shows wide variation among studies, regions, and populations, with risk estimates ranging from 0.99 to 7.83.[7] Study designs with variable case definitions and adjustment for confounders may explain some of these differences.[9] Moreover, biological and nonbiological factors may underlie racial and ethnic differences in the risk of diabetic complications, including cardiovascular disease, retinopathy, nephropathy, and neuropathy.[10] Similar factors could explain differences in DM-associated "immunopathy," leading to increased TB risk. Variables contributing to differential susceptibility probably include local host and pathogen genetics and microbiota, competing acquired risk factors such as HIV, and environmental and behavioral factors (eg, smoking, alcohol consumption, and exposure to outdoor or indoor air pollution). Poor glycemic control, which is associated with TB susceptibility,[8] is also a reflection of access to effective DM care.[11] Studies indicate that South India, the Pacific Islands, and Mexico are particular hotspots for DM-associated TB.[12] For example, it was recently reported that 54% of adult patients with newly diagnosed TB in Chennai, India have DM, whereas only 25% were normoglycemic.[13] In some Pacific islands, approximately 40% of patients with TB have concurrent DM,[14] and at the Texas-Mexico border region it is about 25%.[15] There is accumulating evidence that DM is associated with drug-resistant and multidrug-resistant TB (MDR-TB).[16,17] It is unclear to what extent growing DM prevalence rates contribute to the increasing burden of difficult to treat MDR-TB globally (estimated at 580,000 in 2015).[18]

It is generally assumed that DM is increasing the risk of TB rather than TB increasing the likelihood of DM

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developing.[9,19] However, many studies have been unable to ascertain if the onset of DM predated TB infection,[9] even when it is clear that DM developed before active TB.[12] It is also plausible that TB may increase DM risk. A previous TB diagnosis was associated with an increased risk of DM over a 4-year period based on primary care data in the United Kingdom, although this study could have been affected by residual confounding.[20] In an Indian cohort study, patients with TB with newly diagnosed DM had markedly lower glycated hemoglobin (HbA1c) values (although still abnormal) compared with those with known DM, suggesting that TB might, at least transiently, stimulate progression from intermediate hyperglycemia to frank DM or identify those individuals who may be more prone to metabolic alterations or diabetes in the future.[13] However, there are no cohort studies following patients in whom transient hyperglycemia developed during TB treatment over the longer term (5-10 years) to assess their future risks of DM, need for DM care, and possible intervention.

Prediabetes, Transient Hyperglycemia, and TB

Prediabetes reflects a continuum of insulin resistance and hyperglycemia that is above "normal" but not reaching the cutoff value for DM.[21] Prediabetes might also be associated with increased risk of TB and adverse TB outcomes, although evidence is limited. Studies from both India and South Africa have found an extremely high prevalence of prediabetes defined by HbA1c or a oral glucose tolerance test (OGTT) among patients with TB of 25% to 57%.[13,22,23] A recent cross-sectional study among refugees arriving in the United States also found an increased prevalence of latent TB infection (LTBI) among individuals with prediabetes (39.1%) and DM (43.4%) compared with those with normoglycemia (25.9%), with even higher prevalences for those who also had low vitamin D levels.[24] Only a few studies have published data estimating the association between prediabetes and active TB; one Indonesian study found a significant association between impaired fasting blood glucose levels and TB (OR, 4.2; 95% CI, 1.5-11.2),[25] and two other studies from the United States and China also reported associations of 1.34 using OGTT[26] and 1.14 based on impaired fasting blood glucose levels,[27] but the US study was underpowered and neither was statistically significant. Further observational evidence of the effects of prediabetes on TB risk and outcomes is needed.

In low-income settings, DM is often undiagnosed, but results of screening tests during active TB may be harder to interpret due to inflammation- or stress-related hyperglycemia. Even though transient, this hyperglycemia not only is associated with adverse TB outcomes[28] but also is a marker for a future risk of type 2 DM, similar to gestational DM.[29]

Population Impact of DM on TB

Several studies have estimated the population impact of DM on TB, often in comparison with other TB risk factors such as HIV, smoking, malnutrition, and indoor air quality.[30] Generally, between 10% and 20% of TB is attributed to DM,[31,32] although specific settings reported higher risks.[12] Such studies, although mathematically simple, are hampered by conceptual difficulties[33] and are likely to result in inaccurate estimates of the true population impact of DM. This is because they are "static" and fail to account for possible higher TB transmission associated with DM. More dynamic models of TB and DM have been developed,[34] demonstrating the potential benefits of controlling DM to mitigate the burden of TB. A recent mathematical modeling study representing 13 countries with high TB burdens estimated that if the prevalence of DM continues to rise at present rates, global TB incidence would decline by only 8.8% and TB mortality would decline by 34.0% by 2035. If DM prevalence stopped increasing, TB would decline by 20.3% and mortality would decline by 42.7%. Moreover, if the prevalence of DM increases further, the declining trends in TB incidence will be reversed entirely, and by 2035 there would be a 7.8% increase in TB incidence.[34] All modeling studies also suffer from data limitations; robust estimates for all key parameters (such as associations between DM and LTBI) are not currently available and may be refined in the future. Emerging evidence that DM is associated with MDR-TB will also need to be incorporated into future models.[16,17] Continued attempts to refine the population impact of DM on TB are essential to estimate the cost-effectiveness of potential interventions focused on DM compared with targeting other TB risk factors[30] or intensifying screening and case finding.

Obesity, Nutritional Status, and TB-DM

Nutritional status is an important factor in the association of TB and DM.[35] Undernutrition, with respect to both total nutrient intake and specific micronutrients, is inversely associated with TB risk in observational studies.[36] Conversely, obesity increases DM risk, but overweight (with higher BMI, at least up to

30 kg/m^2) without DM appears to be protective against TB.[37] In any given population, only a fraction of those individuals with high BMI will acquire DM; hence, the population impact of rising BMI on TB is not clear, although it is important to note that DM risk increases at much lower levels of BMI in individuals from Asian countries than in people from Western countries.[38] Recent systematic reviews of macronutrient supplementation among patients with TB have not shown treatment benefit, but there are only a few small low-quality trials available.[39]

Specific micronutrients, as well as total calorie consumption, have been implicated in TB risk, but there is as yet no strong evidence that supplementation improves TB outcomes.[39] Vitamin D deficiency can be very common; a recent Indian study found that 100% of patients with TB-DM have insufficient vitamin D levels.[13] There has been much speculation about the potential role of vitamin D supplementation in reducing infection risks or improving outcomes in patients with TB or DM, with little evidence of benefit,[40,41] although better designed studies are under way (eg, http://www.d2dstudy.org).

Further observational studies are needed to better understand the interactions between TB and DM over a range of BMI values in different populations, as well as to determine optimal BMI ranges and specific macro- or micronutrients that may be involved in reducing TB risks in different populations of patients with DM. Further trials of the effects of micronutrient supplementation on TB recurrence and LTBI reactivation may also be warranted, including in patients with DM.

HIV and Diabetes (and TB)

Little is known about how HIV may affect the interaction between TB and DM. The association between TB and HIV was well recognized from the early years of the AIDS epidemic, with the greatest burden of TB-HIV coinfection being in Sub-Saharan Africa.[42] With mortality from HIV falling in Sub-Saharan Africa and increasing prevalence of noncommunicable diseases (NCDs), it is likely that the prevalence of DM in patients with HIV is rising.[42,43] In addition, ART, especially with protease inhibitors, increases the risks of metabolic syndrome, dysglycemia, and subsequently DM and cardiovascular disease,[44-46] particularly as use increases over time with improved HIV survival. However, studies of patients with HIV from Sub-Saharan Africa have shown substantial heterogeneity in DM prevalence, possibly due to differences in settings (hospital or community-based), methods for ascertaining DM, and diagnostic cut points used, as well as whether the HIV-infected participants included had already received ART.[47] Diabetes prevalence among cohorts of patients with HIV has thus varied from 0% to 10%, and dysglycemia prevalence has ranged from 2% to 35%.[47] There may be a different association between TB and DM in people with HIV.[48] A Tanzanian cohort study demonstrated a fivefold increased risk of early mortality among HIV-uninfected patients but only a twofold increase among HIV confected patients.[49] The precise explanations for this are uncertain, but the very strong association between HIV and TB may suppress that of DM, given that HIV is associated with reduced long-term survival, poorer nutritional status, and lower BMI, all reducing the opportunity for DM to develop. Cotrimoxazole prophylaxis for infections in HIV-infected patients also has hypoglycemic effects and may be protective against DM.[50] Despite the potential public health importance, there is limited modeling or projections of the likely future of DM, HIV, and TB multimorbidity in Sub-Saharan Africa or elsewhere. There is also little evidence for the optimal screening and management of DM in patients with HIV, although it is thought that DM is currently underdiagnosed and improperly managed in patients with HIV as well as in patients with TB.

Prevention of DM

To date, efforts to control the converging epidemics of DM and TB have focused on detection and treatment rather than DM prevention, the latter of which is very difficult. In one of the largest clinical trials, the Diabetes Prevention Program, a labor-intensive lifestyle change program and use of metformin showed a 31% to 58% reduction in short-term DM incidence, but long-term follow-up revealed that DM was merely delayed,[51] and such intensive individually focused programs could not be generalized in low-income settings. More effective approaches may include environmental change or fiscal and legislative change (eg, taxes on fast food and sugar and improved community-planning laws), but there is limited evidence for their effectiveness.[52,53] Unfortunately, prevention of NCDs has a low priority in TB-endemic settings due to low awareness and a high burden of communicable or acute illnesses. Besides primary prevention, the early detection and treatment of DM as well as interventions to lower HbA1c in patients with diabetes (lifestyle interventions or medication), could reduce TB risk, although evidence for this is limited.[54]

Detection and Clinical Management of TB-DM

Screening Patients With TB for DM and Patients With DM for TB

Detection of combined TB and DM is a first step toward better disease management. The prevalence of DM among patients with TB varies across settings but is generally > 10% and often much higher, especially in older age groups, with up to 50% of cases newly detected on screening.[22,55,56] Diabetes screening in patients with TB is not straightforward. Diabetes risk scores and different laboratory measurements such as fasting or random blood glucose levels, OGTT, and HbA1c need to be evaluated in different settings and patient populations.[57] There is also a lack of clarity regarding the optimal timing of DM screening, as active TB can induce insulin resistance and stress hyperglycemia.[28] Ongoing studies by the TANDEM project have demonstrated the heterogeneity in diagnostic accuracy of screening algorithms among different populations.[58] In general, point of care HbA1c and blood glucose testing, in combination with age, diagnosed the most patients with DM, but the sensitivity and specificity of these approaches were highly variable.[58]

The yield of TB screening among patients with DM is much lower. When TB prevalence is < 25 per 100,000, at least 1,000 people with DM would need to be screened to detect a single additional case of TB.[59] In contrast, in countries like India, screening 90 to 350 people with DM would be expected to yield one or more TB cases.[60] Risk stratification (including background TB prevalence, history of TB, DM "severity," smoking, socioeconomic variables, and presence of cough) could help prioritize a subgroup of patients with DM for TB screening. Again, more data are needed regarding the most optimal screening tools (questionnaires, microbiological tests, and chest radiographs) for TB in diabetes or general medicine clinics. New developments, such as computer-assisted radiography reading,[61] may help facilitate screening patients with DM for TB in some high-incidence settings, but at present, this is highly unlikely to be a cost-effective approach.

Screening Patients With DM for LTBI

Screening and treatment of LTBI has been advocated for groups at high risk for the development of active TB, for example, in HIV-infected individuals. This approach may theoretically help progress toward TB elimination in some higher-income settings in which a high proportion of TB cases arise from reactivation among foreign-born migrants with DM, suggesting that this group may be an appropriate population on which to focus LTBI screening.[59,62] LTBI diagnosis is very important and should precede treatment. However, the few studies in the literature on the impact of DM on TB are small and show contradictory results regarding the QuantiFERON test (Qiagen) in patients with DM.[63-65] Immune-based tests do not predict TB very well. Currently there is no evidence that LTBI treatment is effective among people with DM or if it leads to more isoniazid hepatotoxicity or lower drug levels. No cost-effectiveness studies have been done, and it is unclear how to counsel providers to test and treat LTBI or how to encourage patients with DM to accept and adhere to LTBI treatment.

Clinical Management of Combined TB and DM

Most studies of TB and DM have focused on prevalence or screening, and there are very little data to guide clinical management of patients with the two diseases. A number of questions remain to be answered[66]:

1. Should we adjust TB treatment in dose or duration? Should we follow TB-DM patients after completion of TB treatment given the higher risk of recurrent TB?
2. How important is glycemic control for improving TB outcomes in TB-DM?
   Should we use insulin or metformin (or other glucose-lowering medications) for glycemic control in patients with TB-DM?
3. Is there more hepatotoxicity in TB-DM? Should we monitor TB treatment more intensively in patients with TB-DM?
4. What drug-drug interactions are relevant for treating combined TB-DM?
5. Can we explain the higher mortality seen in TB-DM in some settings? Should we consider adjuvant anti-platelet or lipid-lowering treatment?
6. How should patients with TB-DM be counseled regarding lifestyle changes?
7. How should care for patients with TB-DM be coordinated, and how should DM care be continued after completion of TB treatment?

Patients with DM are generally more likely to experience TB treatment failures and recurrences.[16] Observational studies suggest that prolonged treatment may improve outcomes.[67] Some studies found lower concentrations of rifampicin and other TB drugs in patients with diabetes,[68] suggesting that higher drug dosages[69,70] may be of benefit. This could, however, lead to more drug toxicity and treatment complications, especially in patients with TB-DM, who are generally older and often

have pre-existing liver or kidney disease. There is now good evidence that diabetes is a risk factor for drug-resistant TB,[17] but there are no systematic data on the use of second-line TB drugs in individuals with DM.

There is also a lack of evidence to guide DM management in patients with TB-DM. Diabetes is not a homogeneous disease. Patients have different levels and durations of hyperglycemia, hyperlipidemia, inflammation ("metaflammation"), body composition, cardiovascular risk profiles, medications, complications, comorbidities, and ethnic backgrounds. Achieving good glycemic control in TB-DM is challenging because of inflammation, drug-drug interactions, and other issues,[6] and the benefit of tight or even improved glucose control during TB treatment remains to be determined. Rifampicin strongly increases the metabolism of most oral antidiabetes drugs,[6] whereas insulin, advocated in guidelines for TB-DM, has several drawbacks, including its insecure availability in many settings,[71] risks of hypoglycemia, and need for drug injection and self-measurement of blood glucose. Metformin, a widely used oral drug for type 2 DM, probably has no drug interaction with rifampicin and does not typically induce hypoglycemia. However, its safety and tolerability in patients with TB has not been investigated.

Drug-drug interactions may occur during absorption, distribution, liver metabolism, and elimination from the kidney. Several drug-drug interactions are of concern in managing patients with TB and DM or HIV, or a combination. Rifampicin as a primary TB drug can affect the efficacy of many other drugs, including HIV drugs and most oral DM drugs.[6] Dolutegravir, one of the most widely prescribed anti-HIV drugs, blocks metformin elimination and thus doubles metformin exposure,[72] which may lead to lactic acidosis. All these interactions show large interindividual variability, and there is a lack of pharmacokinetic studies in this field.

Besides glycemic control, other treatment options may have to be considered in patients with TB-DM. For example, studies in Taiwan[73] and Tanzania[49] showed increased early (< 3 months) mortality, which could be caused by cardiovascular events. If true, there should be more awareness regarding cardiovascular risk management, with the possible use of antiplatelet, lipid-lowering, and antihypertensive treatments, as well as lifestyle interventions, especially smoking cessation.[6] Timing of interventions targeting TB and DM should also be examined. All these questions could be addressed in pragmatic clinical trials, but to our knowledge, so far only one trial by the TANDEM project, is ongoing (NCT02106039).

Health Systems Challenges

Health systems issues in managing TB and DM together may be among the greatest challenges to overcome.[74] Continued management of DM by itself is a particular problem in most low- and middle-income countries because of lack of health insurance coverage and the fact that health systems in these settings are not designed for the management of chronic conditions such as DM.[75] Although directly observed short-course treatment for TB (DOTS) and World Health Organization funding have substantially improved uptake and outcomes of TB treatment, no such equivalents for DM care exist in low-income settings, and hence levels of DM detection and management are generally poor.[36] Moreover, political will or comprehensive national strategies are often lacking, management guidelines are not widely available, and staff may be scarce or poorly trained. The general trend toward an expansion of the private sector as a provider of NCD care in urban areas often exacerbates inequality, leaving an underclass of the most deprived patients with DM accessing increasingly rundown state services[74]; such groups are also at highest risk of TB. Relatively few lower-income countries have developed comprehensive strategies to reduce the upstream determinants of DM, such as obesity, poor diet, and physical inactivity, with little intersectoral collaboration.[76] This is despite alarming predictions of rising DM prevalence and associated costs. Some countries (eg, India, China) have established policies and mechanisms for screening patients with TB for DM, including establishing blood glucose testing and in some cases providing insulin in TB clinics,[77,78] but generalizing these processes across the entire country has not yet been successful.

Summary and Future Research Priorities

DM is an increasingly important factor contributing to the global TB epidemic. There are a number of outstanding questions regarding the epidemiology of the interaction between TB and DM, its clinical management, and public health aspects.

Regarding epidemiology, better-designed epidemiologic studies and clinical cohorts are required to better understand the importance of transient hyperglycemia, the magnitude of the association between DM and

drug-resistant TB, and the potential impact of rising DM prevalence on "difficult to treat" MDR-TB.

Regarding clinical management, clinical trials or large cohort studies should examine the benefit of prolonged or intensified TB treatment for patients with TB-DM and clinically relevant interventions with respect to DM (eg, best approaches for glycemic control, follow-up of patients with transient hyperglycemia, management of cardiovascular risk, optimal timing and methods of screening for DM) for the full range of patients with TB-DM and across different ethnicities.

Regarding public health, more refined mathematical and economic models are required to estimate the costs and potential impact of different interventions (such as screening patients with TB for DM and vice versa, intensified management, and treatment of LTBI) on the TB epidemic in different populations. Cost-effectiveness analyses are entirely lacking at present, and our list of priorities may need to be reconsidered as such studies become available.

Diabetes is not a homogeneous disease (as is the case for TB). Differences in duration and severity of hyperglycemia, hyperlipidemia, inflammation (metaflammation), body composition, cardiovascular risk profiles, smoking behavior, medication, complications and comorbidities, ethnic backgrounds, socioeconomic status, and access to health care probably account for variable effects of DM on TB risk and TB treatment outcomes. Furthermore, HIV is becoming an increasingly important cofactor in this interaction, especially with the increasing prevalence of DM in Sub-Saharan Africa. This should be taken into account in future research.

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