**Defining a research agenda to address the converging epidemics of tuberculosis and diabetes. Part 1: Epidemiology and clinical management**

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**Abstract**

There is growing interest in the interaction between type 2 diabetes (DM) and tuberculosis (TB), but many research questions remain unanswered. Epidemiological, basic science and clinical experts recently convened and identified priorities. This is the first of two reviews on this topic, summarising priority areas of research with regard to the epidemiology, clinical management and public health. *First*, from an epidemiological point of view, more study is needed to determine the importance of transient hyperglycemia in TB patients, and on the importance of DM for the global epidemic of multi-drug resistant (MDR)-TB. *Second,* with regard to screening and clinical management of combined TB-DM, cas well as prolonged or intensified TB treatment for outcome of TB-DM, and investigate cost-effectiveness of screening methods for DM among newly diagnosed TB patients. *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 systems interventions should be developed for routine TB-DM screening, management of DM after TB treatment completion, and better access to DM services worldwide. Studies are needed across different ethnicities and settings, given the heterogeneity of metabolic perturbations, inflammation, 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.

# Introduction

Prevalence of type 2 diabetes (DM) continues to increase rapidly in low and middle income countries (LMIC) as a result of rapid urbanisation[1](#_ENREF_1) and nutrition transition[2](#_ENREF_2), combined with a genetic and epigenetic ‘mismatch’ of their inhabitants with more affluent environments[3](#_ENREF_3). Already, about 80% of the 415 million estimated DM cases globally are from LMICs. Diabetes increases the risk of many infectious diseases including tuberculosis[4](#_ENREF_4) (TB), and diabetes prevalence is projected to rise most steeply in regions with high TB incidence such as Sub-Saharan Africa (SSA) over the next 30 years[5](#_ENREF_5). A high proportion of diabetes in LMICs is undiagnosed and diabetes screening can be more challenging during TB treatment due to stress hyperglycemia that might be transient[6](#_ENREF_6). Optimal TB treatment regimes for diabetic patients have not been established, and many issues related to DM management during TB treatment remain unresolved. The scale of the health systems challenges with regard to the interacting epidemics of TB and DM have 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 non-communicable diseases with regard to their epidemiology, underlying biological mechanisms and clinical management. This review provides an overview of the topics discussed, ending with a list of research prioirities, with Part 1 focussing on the epidemiology, public health and clinical aspects of the TB-DM interaction.

# Epidemiology and public health

**Summary box**

* **Diabetes increases risks of TB disease and poor TB treatment outcomes**
* **There is a relationship between dysglycaemia and TB risk**
* **Improved nutrition (and higher Body Mass Index - BMI) is protective against TB; hence at a population level the interplay between rising obesity and TB disease 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 HIV patients appears to be high, particularly among those on anti-retroviral therapies (ART)**
* **The interactions among DM, HIV and TB are multi-dimentional 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 over a three-fold increased risk of TB disease among DM patients[7](#_ENREF_7), and a doubling of prolonged sputum positivity, TB treatment failure, death, and relapse[8](#_ENREF_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](#_ENREF_7). Study designs with variable case definitions and adjustment for confounders may explain some of these differences[9](#_ENREF_9). Moreover, biological and non-biological factors may underlie racial and ethnic differences in the risk of diabetic complications including cardiovascular disease, retinopathy, nephropathy and neuropathy[10](#_ENREF_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 like HIV, and environmental and behavioral factors (e.g., smoking, alcohol consumption, and exposure to outdoor or indoor air pollution). Poor glycemic control, which is associated with TB susceptibility[8](#_ENREF_8), is also a reflection of access to effective DM care[11](#_ENREF_11). Recent studies indicate that South India, the Pacific Islands and Mexico are particular hotspots for DM-associated TB.[12](#_ENREF_12) As an example, it was recently reported that 54% of newly diagnosed adult TB patients in Chennai, India, have DM while only 25% were normoglycemic[13](#_ENREF_13). In some Pacific islands around 40% of TB patients may have concurrent DM[14](#_ENREF_14), and about 25% in the Texas-Mexico border region have DM[15](#_ENREF_15). There is accumulating evidence that DM is associated with drug-resistant and multi-drug-resistant TB (MDRTB)[16](#_ENREF_16),[17](#_ENREF_17), It is unclear to what extent growing DM prevalence rates contribute to the the increasing incidence of difficult-to-treat MDRTB globally (estimated at 580,000 in 2015)[18](#_ENREF_18).

It is generally assumed that DM is increasing the risk of TB, rather than TB disease increasing the likelihood of developing DM.[9](#_ENREF_9),[19](#_ENREF_19) However, many studies have been unable to ascertain if the onset of DM pre-dated TB infection,[9](#_ENREF_9) even when it is clear that DM developed before active TB disease[12](#_ENREF_12). It is also plausible that TB disease may increase DM risk. A previous TB diagnosis was associated with an increased risk of DM over a four year time period based on primary care data in the UK, though this study could have been affected by residual confounding[20](#_ENREF_20). In an Indian cohort study, TB patients with newly diagnosed DM had markedly lower glycated haemoglobin (HbA1c) values (although still abnormal) compared to those with known DM, suggesting that TB might, at least traniently, stimulate progression from intermediate hyperglycaemia to frank DM or identify those individuals who may be more prone to metabolic alterations or diabetes in the future[13](#_ENREF_13). However, there are no cohort studies following up patients who developed transient hyperglycaemia during TB treatment over the longer term (5-10 years), to assess their future risks of DM, need for DM care, and possible intervention.

## Pre-diabetes, transient hyperglycemia and TB

Pre-diabetes reflects a continuum of insulin resistance and hyperglycaemia that are above “normal” but not reaching the cut-off for DM.[21](#_ENREF_21) Pre-diabetes might also be associated with increased risk of TB disease and adverse TB outcomes, although evidence is limited. Studies from both India and South Africa have found extremely high prevalence of pre-diabetes defined by HbA1c or oral glucose tolerance test (OGTT) among TB patients of 25%-57%[22](#_ENREF_22) [13](#_ENREF_13),[23](#_ENREF_23). A recent cross-sectional study among refugees arriving into the US also found increased prevalence of latent TB infection (LTBI) among individuals with pre-diabetes (39.1%) and DM (43.4%) compared to those with normal glycaemia (25.9%), with even higher prevalences for those who also had low vitamin D levels.[24](#_ENREF_24) Only a few studies have published data estimating the association between pre-diabetes and active TB; one Indonesian study found a significant association between impaired fasting blood glucose (FBG) and TB (OR 4.2, 95% CI 1.5 to 11.2)[25](#_ENREF_25), and two other studies from the US and China also reported associations of 1.34 using OGTT[26](#_ENREF_26) and 1.14 based on impaired FBG[27](#_ENREF_27) but the US study was underpowered, and neither were statistically significant. Further observational evidence of the effects of pre-diabetes 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 hyperglycaemia is not only associated with adverse TB outcomes[28](#_ENREF_28), but also a marker for future risk of type 2 DM, similar to gestational DM[29](#_ENREF_29).

Population impact of DM onTB

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](#_ENREF_30" \o "Lonnroth, 2009 #29). Generally, between 10-20% of TB is attributed to DM[31](#_ENREF_31" \o "Stevenson, 2007 #30),[32](#_ENREF_32" \o "Walker, 2010 #31), although specific settings reported higher risks[12](#_ENREF_12" \o "Restrepo, 2011 #12). Such studies, although mathematically simple, are hampered by conceptual difficulties[33](#_ENREF_33" \o "Rockhill, 1998 #25) and 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](#_ENREF_34" \o "Koo, 2013 #33), demonstrating the potential benefits of controlling DM to mitigate the burden of TB. A recent mathematical modelling 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 by 34.0% by 2035. If DM prevalence stopped increasing, TB would decline by 20.3% and mortality 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.[35](#_ENREF_35" \o "Pan,  #27) All modelling 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 MDRTB will also need to be incorporated into future models[16](#_ENREF_16" \o "Baker, 2011 #9),[17](#_ENREF_17" \o "Huangfu P, 2016 #10). 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](#_ENREF_30" \o "Lonnroth, 2009 #29) 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[36](#_ENREF_36" \o "Odone, 2014 #31). Undernutrition, both in terms of total nutrient intake and specific micronutrients, is inversely associated with TB risk in observational studies[37](#_ENREF_37). Obesity on the other hand increases DM risk, but overweight (with higher BMI, at least up to 30 kg/m2) without DM appears to be protective against TB.[38](#_ENREF_38) In any given population, only a fraction of those individuals with high BMI will develop DM, and hence the population impact of rising BMI on TB is not clear, though it is important to note that DM risk increases at much lower levels of BMI in individuals from Asian countries than in the West[39](#_ENREF_39). Recent systematic reviews of macronutrient supplementation among TB patients have not shown treatment benefit, but there are only a few, small low quality trials available[40](#_ENREF_40).

Specific micronutrients, as well as total calorie consumption, have been implicated in TB risk, but there is as yet no strong evidence that supplementation might improve TB outcomes[40](#_ENREF_40). 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[41](#_ENREF_41),[42](#_ENREF_42) although better designed studies are underway (see for example: <http://www.d2ds>tudy.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 determining optimal BMI ranges and specific macro- or micronutrients that may be involved in reducing TB risks in different populations of DM patients. Further trials of the effects of micro nutrient supplementation on TB recurrence and LTBI reactivation may also be warranted, including DM patients.

## 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 recognised from the early years of the AIDS epidemic, with the greatest burden of TB-HIV co-infection being in SSA[43](#_ENREF_43). With mortality from HIV falling in SSA, and increasing prevalence of non-communicable diseases (NCDs), it is likely that the prevalence of DM in HIV patients is rising[43](#_ENREF_43),[44](#_ENREF_44). In addition, ART, especially protease inhibitors, increases the risks of metabolic syndrome, dysglycaemia and subsequently DM and cardiovascular disease[45-47](#_ENREF_45), particularly as use increases over time with improved HIV survival. However, studies of HIV patients from SSA 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[48](#_ENREF_48). Diabetes prevalence among cohorts of HIV patients has thus varied from 0-10% and dysglycaemia prevalence from 2-35%, respectively[48](#_ENREF_48" \o "NigatuHaregu, 2012 #73). There may be a different assocation between TB and DM in people with HIV[49](#_ENREF_49). A Tanzanian cohort study demonstrated a fivefold increased risk of early mortality among HIV-uninfected patients, but only a twofold increase among HIV co-infected patients.[50](#_ENREF_50) 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. Co-trimoxazole prophylaxis for infections in HIV-infected patients also has hypoglycaemic effects, and may be protective against DM[51](#_ENREF_51). Despite the potential public health importance, there is limited modelling or projections of the likely future of DM, HIV and TB multi-morbidity in SSA or elsewhere. There is also little evidence for the optimal screening and management of DM in HIV patients, although it is thought that DM is currently under-diagnosed and improperly managed in HIV as well as in TB patients.

me[52](#_ENREF_52" \o "Hamman, 2015 #56)change limited [53](#_ENREF_53" \o "Capewell, 2011 #57),[54](#_ENREF_54" \o "Ghandour, 2015 #95)[55](#_ENREF_55" \o "Pearson-Stuttard,  #59)

# Detection and clinical management of TB-DM

## Screening TB patients for DM and DM patients for TB

Detection of combined TB and DM is a first step towards better disease management. The prevalence of DM among TB patients 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](#_ENREF_22),[56](#_ENREF_56),[57](#_ENREF_57). Diabetes screening in TB patients is not straightforward. Diabetes risk scores and different laboratory measurements like fasting or random blood glucose levels, OGTT and HbA1c need to be evaluated in different settings and patient populations[58](#_ENREF_58). 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](#_ENREF_28) Ongoing TANDEM studies have demonstrated the heterogeneity in diagnostic accuracy of screening algorithms among different populations[59](#_ENREF_59). In general, point of care HbA1c and blood glucose testing, in combination with age, diagnosed the most DM patients, but the sensivity and specificity of these approaches were highly variable[59](#_ENREF_59).

The yield of TB screening among patients with DMis much lower. Where TB prevalence is <25 per 100,000, at least 1000 people with DM would need to be screened to detect a single additional case of TB.[60](#_ENREF_60) In contrast, in countries like India, screening 90-350 people with DM would be expected to yield one or more TB cases[61](#_ENREF_61). Risk stratification (including background TB prevalence, history of TB, DM “severity”, smoking, socio-economic variables, and presence of cough) could help prioritise a subgroup of DM patients for TB screening. Again, more data are needed regarding the most optimal screening tools (questionnaires, microbiological tests and chest X-rays) for TB in diabetes or general medicine clinics. New developments, such as computer-assisted X-ray reading[62](#_ENREF_62), may help facilitate screening DM patients for TB in some high incidence settings; but, at present, this is highly unlikely to be a cost-effective approach.

## Spatients with DM

[60](#_ENREF_60" \o "Demlow, 2015 #60),[63](#_ENREF_63" \o "Barry, 2016 #61)[64-66](#_ENREF_64" \o "Choi, 2015 #62)

## 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[67](#_ENREF_67) **(text box)**.

**Text box**

* **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?**
* **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 TB-DM patients?**
* **Is there more hepatotoxicity in TB‐DM? Should we monitor TB treatment more intensively in a TB‐DM patients?**
* **What drug-drug interactions are relevant for treating combined TB-DM?**
* **Can we explain the higher mortality seen in TB‐DM in some settings? Should we consider adjuvant anti-platelet or lipid-lowering treatment?**
* **How should TB-DM patients be counselled with respect to lifestyle changes?**
* **How should care for TB-DM patients 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](#_ENREF_16). Observational studies suggest that prolonged treatment may improve outcome[68](#_ENREF_68). Some studies found lower concentrations of rifampicin and other TB drugs in diabetics[69](#_ENREF_69) suggesting higher drug dosages[70](#_ENREF_70),[71](#_ENREF_71) may be of benefit. This could however lead to more drug toxicity and treatment complications, especially in TB-DM patients 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](#_ENREF_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 TB-DM patients. Diabetes is not a homogeneous disease. Patients have different levels and duration of hyperglycemia, hyperlipidemia, inflammation (‘metaflammation’), body composition, cardiovascular risk profiles, medications, complications, comorbidity and ethnic backgrounds. Achieving good glycemic control in TB-DM is challenging because of inflammation, drug-drug interactions and other issues[6](#_ENREF_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 antidiabetic drugs[6](#_ENREF_6) while insulin, advocated in guidelines for TB-DM, has several drawbacks including its insecure availability in many settings[72](#_ENREF_72), 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 TB patients 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 and/or HIV. Rifampicin as a primary TB drug can affect the efficacy of many other drugs, including HIV drugs and most oral DM drugs[6](#_ENREF_6). Dolutegravir, one of the most widely prescribed anti-HIV drugs, blocks metformin elimination and thus doubles metformin exposure[73](#_ENREF_73), which may lead to lactic acidosis. All of these interactions show large inter-individual variability and there is a lack of pharmacokinetic studies in this field.

Besides glycemic control, other treatment options may have to be considered in TB-DM patients. For example, studies in Taiwan[74](#_ENREF_74) and Tanzania[50](#_ENREF_50) 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 anti-platelet, lipid-lowering and anti-hypertensive treatments, as well as lifestyle interventions, especially smoking cessation[6](#_ENREF_6). Timing of interventions targeting TB and DM should also be examined. All of these questions could be addressed in pragmatic clinical trials, but to our knowledge, so far only one trial by the TANDEM network, is ongoing (NCT02106039).

## Health systems challenges

Health systems issues in jointly managing TB and DM may be among the greatest challenges to overcome[75](#_ENREF_75). Continued management of DM by itself is a particular problem in most LMICs because of lack of health insurance coverage, and the fact that health systems in these settings are not designed for management of chronic conditions such as DM[76](#_ENREF_76). While directly observed short-course treatment for TB (DOTS) and WHO funding have substantially improved uptake and outcome 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[37](#_ENREF_37). 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 towards an expansion of the private sector as a provider for NCD care in urban areas often exacerbates inequality, leaving an underclass of the most deprived DM patients accessing increasingly rundown state services[75](#_ENREF_75" \o "Phillimore, 2013 #100); 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 inter-sectoral collaboration[77](#_ENREF_77). This is despite alarming predictions of rising DM prevalence and associated costs. Some countries (e.g., India, China) have established policies and mechanisms for screening TB patients for DM, including establishing blood glucose testing and in some cases providing insulin availability in TB clinics[78](#_ENREF_78),[79](#_ENREF_79) but generalising these processes across the entire country has not yet been successful.

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# Summary and future research priorities

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

With regard to epidemiology, better designed epidemiological studies and clinical cohorts are required to better understand the relevance of transient hyperglycemia, the magnitude of the association between DM and drug resistant TB, as well as the potential impact of rising DM prevalence on “difficult to treat” MDRTB.

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

With regard to public health, f

Diabetes is not a homogeneous disease. Differences in duration and severity of hyperglycemia, hyperlipidemia, inflammation (‘metaflammation’), body composition, cardiovascular risk profiles, smoking behavior, medication, complications and co-morbidities, ethnic backgrounds, socio-economic status and access to healthcare probably account for variable effects of DM on TB risk and TB treatment outcomes. Furthermore, HIV is becoming an increasingly important co-factor 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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