Published in final edited form as:

Curr Diab Rep. ; 18(9): 71. doi:10.1007/s11892-018-1036-y.

Stress Hyperglycemia in Patients with Tuberculosis Disease: Epidemiology and Clinical Implications

Matthew J. Magee, PhD⁽¹⁾, Argita D. Salindri, MPH⁽¹⁾, Nang Thu Thu Kyaw, MBBS^{(1),(2)}, Sara C. Auld, MD⁽³⁾, J. Sonya Haw, MD⁽⁴⁾, and Guillermo E. Umpierrez, MD, CDE⁽⁴⁾

¹.Division of Epidemiology and Biostatistics, School of Public Health, Georgia State University

².Centre for Operational Research, International Union Against Tuberculosis and Lung Disease (The Union), Myanmar Office

³.Division of Pulmonary, Allergy and Critical Care Medicine, Emory University School of Medicine

⁴.Division of Endocrinology, Metabolism and Lipids, Emory University School of Medicine

Abstract

Purpose of Review: The intersection of tuberculosis (TB) disease and type 2 diabetes mellitus is severely hindering global efforts to reduce TB burdens. Diabetes increases the risk of developing TB disease and negatively impacts TB treatment outcomes including culture conversion time, mortality risk, and TB relapse. Recent evidence also indicate plausible mechanisms by which TB disease may influence the pathogenesis and incidence of diabetes. We review the epidemiology of stress hyperglycemia in patients with TB and the pathophysiologic responses to TB disease that are related to established mechanisms of stress hyperglycemia. We also consider clinical implications of stress hyperglycemia on TB treatment, and the role of TB disease on risk of diabetes post-TB.

Recent Findings: Among patients with TB disease, the development of stress hyperglycemia may influence the clinical manifestation and treatment response of some patients, and can complicate diabetes diagnosis.

Summary: Research is needed to elucidate the relationship between TB disease and stress hyperglycemia and determine the extent to which stress hyperglycemia impacts TB treatment response. Currently there is insufficient data to support clinical recommendations for glucose control among patients with TB disease, representing a major barrier for efforts to improve treatment outcomes for patients with TB and diabetes.

Corresponding author: Matthew J. Magee, Assistant Professor, Division of Epidemiology and Biostatistics, Georgia State University, PO Box 3984, Atlanta, GA, 30302-3984, mjmagee@gsu.edu, Phone: +1 404 413 1797.

AD Salindri, PO Box 3984, Atlanta, GA, 30302-3984; asalindri1@student.gsu.edu

NTT Kyaw, PO Box 3984, Atlanta, GA, 30302-3984; nangthuthukyaw1@student.gsu.edu

SC Auld, Mailstop 1941-001-1AJ, Emory Hospital, 1364 Clifton Rd, Atlanta, GA, 30322; sara.auld@emory.edu

JS Haw, 69 Jesse Hill Jr Dr SE, Glenn Memorial Building, Atlanta, GA 30303; jhaw@emory.edu

GE Umpierrez, 69 Jesse Hill Jr Dr SE, Glenn Memorial Building, Atlanta, GA 30303; geumpie@emory.edu

Conflicts of Interest:

Matthew J. Magee, Argita D. Salindri, Nang Thu Thu Kyaw, Sara C. Auld, J. Sonya Haw, and Guillermo E. Umpierrez declare they have no conflict of interest.

Human and Animal Rights and Informed Consent: This article does not contain any studies with human or animal subjects performed by any of the authors.

Keywords

tuberculosis; stress hyperglycemia; infection

INTRODUCTION

The coexistence of type 2 diabetes mellitus and active tuberculosis (TB) is an increasing public health problem, especially in low and middle-income countries where both diseases are common [1, 2]. Tuberculosis is the leading infectious disease cause of death among adults worldwide. There are 10.4 million incident TB cases each year, and more than 16% of global TB cases result in death, equating to nearly 2 million TB patient deaths annually [3]. Worldwide, the burden of diabetes is increasing at alarming rates—in 2017 there were 425 million adults with prevalent diabetes compared to 285 million in 2010 [4]. Adding to this threat, the overwhelming majority (80%) of adults with diabetes reside in low- and middle-income countries where TB epidemics remain a leading cause of morbidity and mortality [4, 2]. Diabetes increases the likelihood of developing TB disease by approximately 2–3 times [5] and results in poor TB treatment outcomes, doubling the risk of TB mortality and TB relapse [6, 5, 7]. Diabetes' impact on TB control is particularly alarming, as an estimated 11% of all global TB deaths are attributable to diabetes [8].

Diabetes' negative impact on TB risk is well established. In addition, emerging evidence indicates TB disease may increase the risk of diabetes and other non-communicable diseases [9–11]. The host immune response to active TB disease results in a prolonged state of systemic inflammation. While necessary for the immune response to TB disease, this persistent inflammatory state may result in secondary physiologic stress that has untoward negative metabolic effects—such as stress hyperglycemia. Stress hyperglycemia, defined as a transient hyperglycemia induced by acute illness, is distinct from chronic glucose dysregulation of diabetes [12, 13]. Given the increasing global burdens of TB-diabetes comorbidity, further attention is needed to elucidate the role of stress hyperglycemia during TB disease and its impact on TB clinical outcomes and diabetes incidence.

This review focuses on stress hyperglycemia, with or without pre-existing diabetes, in the context of TB disease. The aim of this review is to summarize findings from recent research to provide an up-to-date overview of the relationship between TB disease and stress hyperglycemia. Our review examines the epidemiology of stress hyperglycemia in the context of TB disease, and highlights possible pathophysiologic mechanisms of stress hyperglycemia during TB disease. We also explore the clinical and treatment consequences of stress hyperglycemia and examine the impact of TB-induced stress hyperglycemia on risk of diabetes post TB treatment. We did not conduct a systematic review but have comprehensively searched PubMed, Embase, and Google Scholar databases to summarize the literature, focusing on research published during the past five years.

SECTION 1: EPIDEMIOLOGY OF STRESS HYPERGLYCEMIA DURING ACTIVE TB DISEASE

In the past 5 years, clinical studies have brought much needed attention to the impact of diabetes on TB risk. Awareness of TB-diabetes comorbidity has led to increased screening for diabetes in TB clinics, and new diabetes diagnoses among patients starting TB treatment are common [14, 15]. Among patients with TB disease who are screened and have hyperglycemia at the start of TB treatment, a high proportion (range 8% to 87%) receive a new diabetes diagnosis (not previously known to have diabetes) (Table 1). However, most studies to date have not determined what proportion of these new diabetes diagnoses have diabetic levels of blood glucose due to stress hyperglycemia in response in active TB, and what proportion have previously undiagnosed but pre-existing diabetes. The nature of TB disease is prolonged, with typical treatment duration of 6–8 months for drug sensitive TB and 9–24 months for multidrug-resistant [MDR] TB. Because most existing data on stress hyperglycemia come from critical care patients with acute illness, the natural history and duration of stress hyperglycemia for patients with TB disease may be different given its relative chronic nature. To determine whether a patient with TB has stress hyperglycemia or pre-existing diabetes, clinical studies are needed to monitor glucose levels at regular intervals during TB treatment and for several months after the infection has resolved.

The few studies that measured blood glucose levels at the start of TB treatment and again at follow-up visits during or at the end of TB treatment reported a general decrease in prevalence and severity of hyperglycemia during the course of TB treatment. For example, studies from Iran [16], Pakistan [17], and Tanzania [18] reported >50% of patients with TB and newly diagnosed hyperglycemia reverted blood glucose levels to normal after 3 or 6-months of TB treatment. In contrast, a 2017 study among Chinese patients with TB without previously diagnosed diabetes reported that 80% (16/20) of patients who had initial hyperglycemia (fasting blood glucose [FBG] >110 mg/dL) remained hyperglycemic after 6-months of TB treatment [19]. However, an important limitation of the above mentioned studies was that the use of hypoglycemia agents during TB treatment was not carefully measured. Moreover, existing studies have used various tests to measure blood glucose and at different time intervals, making it difficult to estimate or compare the prevalence of and change in hyperglycemia among patients with TB. An on-going study from Chennai, India that has measured blood glucose levels at the time of TB diagnosis, during treatment, and 1-year after treatment completion is forthcoming and will help to clarify the frequency of stress hyperglycemia during and after TB treatment [20]. In summary, limited studies that monitored changes in blood glucose levels during TB treatment suggest heterogeneity in glucose trajectories, but preliminary data indicate a majority of patients with hyperglycemia (without previously diagnosed diabetes) at the time of TB treatment start may have stress hyperglycemia.

The proportion of patients with TB disease and hyperglycemia that have previously diagnosed diabetes, undiagnosed pre-existing diabetes, or stress hyperglycemia is influenced by a number of population- and individual-level factors. First, structural determinants of health such as healthcare system factors affect availability of and access to primary care and

diabetes screening services, these in turn influence the frequency and distribution of undiagnosed diabetes [21–24]. Many resource-limited settings with high TB burdens do not have healthcare systems with adequate capacity to prevent, screen, and care for diabetes for the general population. Globally, an estimated 46% of adult diabetes cases are undiagnosed and 84% of these patients live in low- and middle-income countries where TB burdens are the greatest [23, 3]. Thus, in settings with limited access to diabetes screening, a higher proportion of patients with TB and hyperglycemia are likely to have undiagnosed pre-existing diabetes. Second, TB disease characteristics including the duration of illness, severity of symptoms, degree of mycobacterial burden, and extent of lung cavitation may be associated with increased frequency and severity of stress hyperglycemia [25, 20]. Third, the quality of TB healthcare programs and access to TB treatment facilities also impact whether patients with TB disease experience diagnostic and treatment delays [26, 27]. Both diagnostic and treatment delays prolong TB disease and lead to worse prognosis, a factor that may also increase the likelihood of stress hyperglycemia. Fourth, the prevalence of other individual factors such as comorbidities (HIV, smoking status, hepatitis), nutrition, health seeking behaviors, and genetic variability all likely contribute to the extent of stress hyperglycemia among patients with TB [23].

SECTION 2: PATHOPHYSIOLOGY OF TB DISEASE AND STRESS HYPERGLYCEMIA

Stress hyperglycemia is a state of dysglycemia resulting from a variety of acute illnesses such as trauma, infection, surgery or myocardial infarction, and typically resolves with the resolution of the precipitant condition. Stress hyperglycemia results from multiple signal pathways including counter regulatory hormones such as glucagon, growth hormone, catecholamine, and cortisol, and cytokines such as tumor necrosis factor (TNF)- α and interleukin (IL)-1 and IL-6. In the absence of definitive studies of TB disease and stress hyperglycemia, we can presume that some hyperglycemia among patients with TB is attributable to acute stress resulting from changes in the host immune, metabolic, and endocrine mechanisms during TB disease (Figure 1). During infections, whether with TB or other pathogens, pro-inflammatory cytokines and stress hormones can drive stress hyperglycemia by increasing hepatic glucose production and peripheral insulin resistance [28–33]. However, in contrast to other acute infections, the endocrine and immune responses in the context of TB disease are more prolonged in nature, as they may be activated during subclinical TB disease, symptomatic TB disease, during anti-TB treatment, and after even after TB treatment [34, 35].

During initial *Mycobacterium tuberculosis* (*Mtb*) infection and during TB disease, pro-inflammatory and anti-inflammatory cytokines such as interleukin (IL)-1, IL-6, IL-10, interferon (IFN)- γ and tumor necrotic factor (TNF)- α are produced. In addition, macrophages generate nitric oxide and reactive oxygen species, T-cells, and natural killer (NK) cells [36, 37]. In the context of obesity-related diabetes, increased pro-inflammatory cytokines, reactive oxygen species, and nitric oxide cause insulin resistance through a cascade of inflammation pathways leading to hyperglycemia [38–40]. Because increased levels of pro-inflammatory cytokines, reactive oxygen species and nitric oxide are hallmark

of the host response to *Mtb*, similar mechanisms of hyperglycemia may be at play among patients with active TB.

Pro-inflammatory cytokines released during TB disease also activate the hypothalamic–pituitary axis, increasing the release of cortisol, prolactin, catecholamine, estradiol, dopamine, epinephrine, norepinephrine, and thyroid and growth hormones, while decreasing production of dehydroepiandrosterone and testosterone [34, 41–45]. A South African study by Opolot et al. in hospitalized patients (n=160) reported that compared to patients with other acute stress conditions (n=89), newly diagnosed smear positive TB patients (n=71) had higher cortisol and dopamine levels than the non-TB group, and higher epinephrine and norepinephrine than normal levels [43]. Another study among newly diagnosed male patients with pulmonary TB (n=30) reported that growth and thyroid hormones, cortisol, estradiol, and prolactin levels were elevated and dehydroepiandrosterone and testosterone level were lower compared to the healthy male control group (n=19) [44]. Because catecholamine, cortisol, growth hormone, dopamine, epinephrine, and norepinephrine concentrations are elevated during TB disease, it is plausible that these elevations result in increased liver and kidney gluconeogenesis and glycogenolysis and insulin resistance in peripheral tissues that can lead to subsequent hyperglycemia [46–48]. In addition, decreased dehydroepiandrosterone and testosterone during TB disease is correlated with insulin resistance which can also indirectly increase the likelihood of hyperglycemia [49–51].

SECTION 3: IMPLICATIONS OF STRESS HYPERGLYCEMIA ON TB TREATMENT OUTCOMES

Despite availability of effective antibiotic treatment regimens, TB is the leading cause of infectious disease death worldwide [52] and the case fatality rate for all TB in 2016 was 16% [3]. Diabetes is a well-established risk factor for adverse TB treatment outcomes (important risk factors also include HIV, smoking, poor nutrition, drug-resistant TB, and others) [53, 54, 6, 55]. A meta-analysis of the effect of diabetes on TB treatment outcomes found that patients with diabetes had approximately twice the odds of death (pooled odds ratio [OR] 2.1, 95% confidence interval [CI] 1.8–2.5) and TB relapse (pooled OR 1.8, 95% CI 1.4–2.3) compared to patients without diabetes [56]. However, the majority of studies that estimated an association between diabetes and adverse TB outcomes did not stratify by previously diagnosed diabetes, undiagnosed pre-existing diabetes, or extent of hyperglycemia, and none have estimated the effect of stress hyperglycemia on TB treatment outcomes [57].

Because prior studies have not rigorously measured stress hyperglycemia in patients with TB disease, it is not possible to directly characterize the relationship between stress hyperglycemia and TB treatment outcomes. Proxies for stress hyperglycemia reported in the published literature include newly diagnosed diabetes and glycemic control. A 2016 cohort study in Chennai by Kornfeld et al. that compared 2-month TB culture conversion among patients with known diabetes to those with newly diagnosed diabetes (at the time of TB diagnosis) did not report significant differences in proportions achieving culture conversion [20, 58]. Yet, a 2015 study from the country of Georgia reported that patients with TB and

newly diagnosed diabetes had significantly increased odds of cavitary disease at the start of TB treatment, a predictor of poor TB outcomes [25]. The relationship between severity of hyperglycemia and TB treatment outcomes is better described than the effect of newly diagnosed diabetes on TB outcomes [59]. For example, Chiang et al. conducted a cohort study in Taiwan and reported lower mortality among patients with diabetes and higher levels of hyperglycemia (HbA1c >9%) compared to lower levels of hyperglycemia (<7%) (mortality 6% vs. 18%) [58]. The same study did not report a meaningful difference in TB failure rate by level of hyperglycemia (3% vs. 4%). However, the Taiwanese study was limited because it did not stratify by history of diabetes diagnosis and excluded patients with stress hyperglycemia. Another study from Peru that measured diabetes medication use among 136 patients with TB and diabetes reported the highest risk of poor TB outcome among those receiving only insulin (38%) during TB treatment as compared to those receiving oral hypoglycemic agents (14%) or both (12%) [60]. Overall, studies that estimated the effects of glycemic levels on TB outcomes have heterogeneous results [57], likely due to the timing of glucose levels measurements, severity of TB disease at baseline, type of diabetes care, and the complex amalgamation of patients with TB and previously diagnosed diabetes, undiagnosed pre-existing diabetes, and stress hyperglycemia.

Clinical Lessons from Critical Care Medicine

Even among patients without TB, treatment and management of stress hyperglycemia in critical care is controversial, in particular whether clinical targets should include tight versus normal glucose control [13]. Generally, the association between stress hyperglycemia and adverse outcomes differs by pre-existing diabetes [61]. Critical care and surgery patients with no history of diabetes or patients with non-insulin treated diabetes are at increased risk of adverse outcomes with increasing levels of hyperglycemia [62, 63]. However, among patients with insulin treated diabetes, there is a U-shaped relationship between risk of adverse outcomes (hospital length of stay, complications, and cost) and maximum glucose level; patients treated to achieve tight glucose control (<180mg/dL maximum glucose) may have higher risk of adverse outcomes [12, 64].

When and how patients with TB and hyperglycemia should be treated to reduce glucose levels remains an urgent gap in knowledge. Based on data from critical care settings, patients with TB and hyperglycemia should be stratified by history of diabetes and history of insulin therapy, as patients with TB and insulin treated diabetes may not benefit from tight glucose control during TB treatment. However, those with newly diagnosed diabetes (or stress hyperglycemia) who achieve tight glucose control may have better TB outcomes, decreased complication rates, and reduced mortality compared to untreated patients. Regardless of the relationship between TB and stress hyperglycemia, there is increasing evidence that all patients with TB disease should be screened for hyperglycemia at the start of TB treatment. At a minimum, patients with TB disease and newly diagnosed hyperglycemia should receive regular glucose monitoring through TB treatment in order to gather more evidence and guide future interventions or clinical trials.

SECTION 4: DIABETES INCIDENCE AFTER SUCCESSFUL TB TREATMENT

The extent to which TB disease can lead to an increased risk of developing diabetes is unknown. The natural history from normoglycemia to diabetes includes several stages, often following a directed pathway from subclinical diabetes to pre-diabetes before developing overt diabetes [65]. In some patients, stress hyperglycemia resulting from TB disease may accelerate or advance the progression from normoglycemia toward pre-diabetes or diabetes. Limited data suggest that for the majority of patients with TB disease and stress hyperglycemia, glucose levels reduce or return to normal during TB treatment or post TB treatment [17, 18, 66]. However, whether stress hyperglycemia during TB disease is an independent risk factor for incident pre-diabetes or diabetes post TB treatment remains unclear.

Animal model studies have demonstrated that TB infection alone is sufficient to induce stress hyperglycemia [67–69]. But studies among humans have not definitively demonstrated that TB disease alone can induce hyperglycemia. Limited observational studies in humans reported increased risk of hyperglycemia and diabetes incidence post TB treatment. For example, observational studies from Pakistan, Iran, and Tanzania reported that a substantial proportion of patients with TB and newly diagnosed hyperglycemia (i.e., new diagnoses of prediabetes or diabetes) at TB initiation had persistent hyperglycemia at the end of TB treatment (proportion range 26 – 43%) [16–18, 70]. However, for how long this persistent hyperglycemia remains post TB treatment has not been evaluated, and existing data cannot distinguish whether newly diagnosed diabetes at the time of TB disease was pre-existing or due to stress hyperglycemia. Furthermore, a population-based study of patients with a history of TB disease from Denmark reported an increased risk of diabetes incidence compared to those without a history of TB disease [71]. In another example, a retrospective study using primary care data from the UK reported that the incidence of diabetes was significantly higher among those who previously had TB disease (pulmonary or extra-pulmonary TB) compared to those without a history of TB (incidence rate ratio range 2.2–5.4) [72]. Lastly, a preliminary retrospective cohort study of patients with history of pulmonary or extrapulmonary TB from Taiwan reported that the incidence rate of diabetes was higher among patients previously treated for TB disease compared to Taiwan’s national diabetes incidence estimates during a similar time period [73].

Although a bi-directional relationship between TB disease and diabetes has been long hypothesized [74], the biological pathways by which TB disease can increase the risk of diabetes remains unclear. One plausible mechanism by which TB disease may lead to diabetes progression post TB treatment is through stress hyperglycemia and persistently elevated blood glucose levels during TB treatment. As an analogy, intensive care unit (ICU) patients with stress hyperglycemia have increased risk of developing diabetes after hospital discharge. A meta-analysis of cohort studies (n=4) that followed ICU patients after discharge reported that stress hyperglycemia, compared to normoglycemia at ICU admission, was significantly associated with diabetes diagnosis 3 months after discharge (pooled OR 3.5, 95%CI 2.0–6.0) [75]. Similarly during TB disease, persistently elevated blood glucose levels may be a biomarker of severe TB clinical manifestation [76–78], suggesting chronic infection. Such patients may experience prolonged proinflammatory response including

stress hyperglycemia. This chronic hyperglycemia during TB disease may be a catalyst for some patients with pre-existing pre-diabetes which advances the disease toward overt diabetes [79] during or after TB treatment. A cohort study conducted in Chennai, India reported that patients with TB and newly diagnosed diabetes had significantly lower HbA1c levels compared to those with known diabetes (i.e., previously diagnosed diabetes) [20], suggesting that TB disease alone might progress patients with elevated blood glucose level prior to TB infection into a diabetes classification at the time of TB treatment initiation. Epigenetic memory is another plausible mechanism by which TB disease may impact diabetes risk after TB treatment [80, 81]. Epigenetics refers to genetic mechanisms that alter gene functions without changing the DNA sequence, these mechanisms include DNA methylation, histone modification, and microRNA (i.e., a group of non-coding RNA molecules)[82]. In gestational diabetes, leptin DNA methylation has been identified as a mechanism of adaptation of increased blood sugar level or impaired glucose metabolism during pregnancy [83]. Leptin is a adipocytokine that is associated with energy metabolism and insulin control [83], and altered leptin signaling may be associated with increased risk of diabetes [84]. Analogous to gestational diabetes, where hyperglycemia during a specified period of time (pregnancy) increases the long-term risk of diabetes incidence, it is plausible that transient or persistent hyperglycemia during or at the end of TB treatment could leave an epigenetic imprint in tissue and vascular cells which in turn affect the expression of the proatherogenic gene even during subsequent normoglycemic periods [80, 85]. Thus, similar to the increased risk of post-partum diabetes among mothers with prior gestational diabetes [86], we would expect to see an increased of diabetes incidence among patients previously treated for TB disease, especially those with persistent hyperglycemia.

Empirical evidence to support the premise that TB disease increases the risk of both hyperglycemia and diabetes remains limited. To date, prospective cohort studies to assess the long-term risk of diabetes post TB treatment are lacking. In addition, differentiating newly diagnosed diabetes due to pre-existing disorders and newly progressed diabetes (TB-induced) remains a challenge. If TB disease increases the risk of diabetes post TB treatment, an estimated 10.4 million of new TB cases diagnosed each year [87] will be at a risk of developing diabetes and would likely contribute to the global burden of diabetes. Collecting TB disease history data within diabetes surveillance systems would be useful to estimate the potential impact of TB on diabetes burdens. If studies determine that TB disease increases the risk of developing diabetes, subsequent research should seek to identify clinical and host characteristics among patients with TB that are associated with the greatest increased risk of diabetes. Risk scores for diabetes incidence among patients with TB will help to target specific diabetes prevention interventions. Bi-directional screening for TB – diabetes (i.e., screening for TB among patients with diabetes and screening for diabetes among patients with TB) has been proposed and may improve disease management for both TB and diabetes [14, 79], but to date has not included systematic screening of patients with history of TB for diabetes. The optimal time and laboratory measure to screen for diabetes among patients with a history of TB is unclear but will likely differ by setting. Point-of-care HbA1c may be programmatically the most feasible and provide high sensitivity, but is likely to cost prohibitive in resource limited regions. Risk scores and screening algorithms with various laboratory measures need to be tested for diabetes diagnostic accuracy and cost effectiveness

among patients with previous history of TB. Importantly, observational epidemiologic studies are needed to establish the effects of TB disease on diabetes incidence before clinical guidelines and public health programs can be developed and evaluated.

CONCLUSION

The growing clinical and public health burden attributed to TB-diabetes comorbidity poses new concerns about the role of stress hyperglycemia during TB and its impact on TB outcomes and post-TB diabetes risk. Many host inflammatory pathways activated in TB disease can drive stress hyperglycemia. Despite the physiological plausibility of TB-induced hyperglycemia, basic descriptive data on the frequency and severity of stress hyperglycemia in patients with TB has yet to be conclusively characterized.

A number of studies have found that a high proportion of patients with TB-diabetes are newly diagnosed with hyperglycemia during or at the start of TB treatment. Therefore, it is plausible that some patients with TB disease who meet diabetes diagnostic criteria do so as a result of TB-induced stress hyperglycemia. Further, the extent of hyperglycemia tends to decrease during TB treatment (among patients with and without previous diabetes diagnosis), but whether these changes in glycemic levels during TB treatment affect treatment outcomes is unknown.

The ability to make recommendations for glucose control among patients with TB-diabetes is critically limited due to existing gaps in knowledge. Each year there are an estimated 1 million new patients with TB-diabetes, yet clinicians treating these patients do not have sufficient data to make an evidence-based decision about how, when, and to what extent to target glucose control. If glucose control targets for patients with TB-diabetes are similar to critically ill patients, efforts to achieve tight glucose control during TB treatment may increase the risk of poor outcomes and ideally should be based on pre-TB levels of hyperglycemia. Finally, the extent to which stress hyperglycemia and chronic dysglycemia impacts future risk of diabetes incidence, diabetes complications, and other non-communicable disease should garner more attention in both the TB and diabetes research communities.

Acknowledgments

Funding Information: This publication was supported by the National Institute Of Allergy And Infectious Diseases of the National Institutes of Health under Award Numbers R03AI133172 (Magee) and K23AI134182 (Auld). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

REFERENCES

Papers of particular interest, published recently, have been highlighted as::

- Of importance

- Of major importance

1. Harries AD, Lin Y, Satyanarayana S, Lonnroth K, Li L, Wilson N et al. The looming epidemic of diabetes-associated tuberculosis: learning lessons from HIV-associated tuberculosis. The

international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2011;15(11):1436-44, i. doi:0503 [pii] 10.5588/ijtld.11.0503.

2. Magee MJ, Narayan KM. Global confluence of infectious and non-communicable diseases - The case of type 2 diabetes. *Prev Med.* 2013;57(3):149–51. doi:10.1016/j.ypmed.2013.05.027S0091-7435(13)00190-4 [pii]. [PubMed: 23747356]
3. WHO. Global tuberculosis report 2017. Geneva: World Health Organization 2017.
4. IDF. Diabetes Atlas, 8th Edition Brussels: International Diabetes Federation 2017.
5. Lee PH, Fu H, Lee MR, Magee M, Lin HH. Tuberculosis and diabetes in low and moderate tuberculosis incidence countries. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2018;22(1):7–16. doi:10.5588/ijtld.17.0329.
6. Baker MA, Harries AD, Jeon CY, Hart JE, Kapur A, Lonnroth K et al. The impact of diabetes on tuberculosis treatment outcomes: A systematic review. *BMC Med.* 2011;9(1):81. doi:1741-7015-9-81 [pii] 10.1186/1741-7015-9-81. [PubMed: 21722362]
7. Jeon CY, Murray MB. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. *PLoS medicine.* 2008;5(7):e152. doi:08-PLME-RA-0743 [pii] 10.1371/journal.pmed.0050152. [PubMed: 18630984]
8. Collaborators GBDT. The global burden of tuberculosis: results from the Global Burden of Disease Study 2015. *The Lancet Infectious diseases.* 2017. doi:10.1016/S1473-3099(17)30703-X.
9. Barron MM, Shaw KM, Bullard KM, Ali MK, Magee MJ. Diabetes is associated with increased prevalence of latent tuberculosis infection: Findings from the National Health and Nutrition Examination Survey, 2011–2012. *Diabetes research and clinical practice.* 2018;139:366–79. doi:10.1016/j.diabres.2018.03.022. [PubMed: 29574108]
10. Hensel RL, Kempker RR, Tapia J, Oladele A, Blumberg HM, Magee MJ. Increased risk of latent tuberculosis infection among persons with pre-diabetes and diabetes mellitus. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2016;20(1):71–8. doi:10.5588/ijtld.15.0457.
11. Huaman MA, Ticona E, Miranda G, Kryscio RJ, Mugruza R, Aranda E et al. The Relationship Between Latent Tuberculosis Infection and Acute Myocardial Infarction. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2018;66(6):886–92. doi:10.1093/cid/cix910. [PubMed: 29069328] A study that reported higher incidence of myocardial infarction among persons with latent TB infection.
12. Greco G, Ferket BS, D'Alessandro DA, Shi W, Horvath KA, Rosen A et al. Diabetes and the Association of Postoperative Hyperglycemia With Clinical and Economic Outcomes in Cardiac Surgery. *Diabetes care.* 2016;39(3):408–17. doi:10.2337/dc15-1817. [PubMed: 26786574] A multicenter cohort study of cardiac surgery patients that demonstrated a U-shaped relationship between glucose levels and severity of hospital outcomes among patients with insulin treated diabetes.
13. Gunst J, Van den Berghe G. Acute severe illness in diabetes patients: is tolerating hyperglycemia beneficial? *J Thorac Dis.* 2016;8(11):3012–5. doi:10.21037/jtd.2016.11.55. [PubMed: 28066571]
14. Jeon CY, Harries AD, Baker MA, Hart JE, Kapur A, Lonnroth K et al. Bi-directional screening for tuberculosis and diabetes: a systematic review. *Trop Med Int Health.* 2010;15(11):1300–14. doi:10.1111/j.1365-3156.2010.02632.x. [PubMed: 20958887]
15. Harries AD, Murray MB, Jeon CY, Ottmani SE, Lonnroth K, Barreto ML et al. Defining the research agenda to reduce the joint burden of disease from diabetes mellitus and tuberculosis. *Tropical medicine & international health : TM & IH.* 2010;15(6):659–63. doi:TMI2523 [pii] 10.1111/j.1365-3156.2010.02523.x. [PubMed: 20406430]
16. Tabarsi P, Baghaei P, Marjani M, Vollmer WM, Masjedi MR, Harries AD. Changes in glycosylated haemoglobin and treatment outcomes in patients with tuberculosis in Iran: a cohort study. *J Diabetes Metab Disord.* 2014;13(1):123. doi:10.1186/s40200-014-0123-0. [PubMed: 25551103]
17. Aftab H, Christensen DL, Ambreen A, Jamil M, Garred P, Petersen JH et al. Tuberculosis-Related Diabetes: Is It Reversible after Complete Treatment? *Am J Trop Med Hyg.* 2017;97(4):1099–102. doi:10.4269/ajtmh.16-0816. [PubMed: 28820679]

- 18•. Boillat-Blanco N, Ramaiya KL, Mganga M, Minja LT, Bovet P, Schindler C et al. Transient Hyperglycemia in Patients With Tuberculosis in Tanzania: Implications for Diabetes Screening Algorithms. *J Infect Dis*. 2016;213(7):1163–72. doi:10.1093/infdis/jiv568. [PubMed: 26609005] A study demonstrating transient hyperglycemia among patients with TB disease.
19. Lin Y, Yuan Y, Zhao X, Liu J, Qiu L, He X et al. The change in blood glucose levels in tuberculosis patients before and during anti-tuberculosis treatment in China. *Glob Health Action*. 2017;10(1):1289737. doi:10.1080/16549716.2017.1289737. [PubMed: 28470109]
- 20•. Kornfeld H, West K, Kane K, Kumpatla S, Zacharias RR, Martinez-Balzano C et al. High Prevalence and Heterogeneity of Diabetes in Patients With TB in South India: A Report from the Effects of Diabetes on Tuberculosis Severity (EDOTS) Study. *Chest*. 2016;149(6):1501–8. doi:10.1016/j.chest.2016.02.675. [PubMed: 26973015] First study that carefully measured new diabetes diagnoses in patients with TB disease and compared culture conversion rates by type of diabetes diagnosis.
21. Clark ML, Utz SW. Social determinants of type 2 diabetes and health in the United States. *World J Diabetes*. 2014;5(3):296–304. doi:10.4239/wjd.v5.i3.296. [PubMed: 24936251]
22. Leahy S OH AM, OL N, Healy M, McCormack M, Kenny RA et al. Prevalence and correlates of diagnosed and undiagnosed type 2 diabetes mellitus and pre-diabetes in older adults: Findings from the Irish Longitudinal Study on Ageing (TILDA). *Diabetes research and clinical practice*. 2015;110(3):241–9. doi:10.1016/j.diabres.2015.10.015. [PubMed: 26520567]
23. Beagley J, Guariguata L, Weil C, Motala AA. Global estimates of undiagnosed diabetes in adults. *Diabetes research and clinical practice*. 2014;103(2):150–60. doi:10.1016/j.diabres.2013.11.001. [PubMed: 24300018]
24. Menke A, Casagrande S, Aviles-Santa ML, Cowie CC. Factors Associated With Being Unaware of Having Diabetes. *Diabetes care*. 2017;40(5):e55–e6. doi:10.2337/dc16-2626. [PubMed: 28289042]
25. Magee MJ, Kempker RR, Kipiani M, Gandhi NR, Darchia L, Tukvadze N et al. Diabetes mellitus is associated with cavities, smear grade, and multidrug-resistant tuberculosis in Georgia. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease*. 2015;19(6):685–92. doi:10.5588/ijtld.14.0811.
26. Cai J, Wang X, Ma A, Wang Q, Han X, Li Y. Factors associated with patient and provider delays for tuberculosis diagnosis and treatment in Asia: a systematic review and meta-analysis. *PloS one*. 2015;10(3):e0120088. doi:10.1371/journal.pone.0120088. [PubMed: 25807385]
27. Li Y, Ehiri J, Tang S, Li D, Bian Y, Lin H et al. Factors associated with patient, and diagnostic delays in Chinese TB patients: a systematic review and meta-analysis. *BMC Med*. 2013;11:156. doi:10.1186/1741-7015-11-156. [PubMed: 23819847]
28. Dungan KM, Braithwaite SS, Preiser J-C. Stress hyperglycaemia. *Lancet*. 2009;373(9677):1798–807. doi:10.1016/S0140-6736(09)60553-5. [PubMed: 19465235]
29. McCowen KC, Malhotra A, Bistran BR. Stress-Induced Hyperglycemia. *Critical Care Clinics*. 2001;17(1):107–24. doi:10.1016/S0749-0704(05)70154-8. [PubMed: 11219223]
30. Leonidou L, Mouzaki A, Michalaki M, DeLastic AL, Kyriazopoulou V, Bassaris HP et al. Cytokine production and hospital mortality in patients with sepsis-induced stress hyperglycemia. *Journal of Infection*. 2007;55(4):340–6. doi:10.1016/j.jinf.2007.05.177. [PubMed: 17631968]
31. Marik PE, Raghavan M. Stress-hyperglycemia, insulin and immunomodulation in sepsis. *Intensive care medicine*. 2004;30(5):748–56. doi:10.1007/s00134-004-2167-y. [PubMed: 14991101]
32. McGuinness OP. Defective glucose homeostasis during infection. *Annu Rev Nutr*. 2005;25:9–35. doi:10.1146/annurev.nutr.24.012003.132159. [PubMed: 16011457]
33. McGuinness OP. Defective glucose homeostasis during infection. *Annu Rev Nutr*. 2005;25:9–35. doi:10.1146/annurev.nutr.24.012003.132159. [PubMed: 16011457]
34. Kleynhans L, Ruzive S, Ehlers L, Thiart L, Chegou NN, Conradie M et al. Changes in Host Immune–Endocrine Relationships during Tuberculosis Treatment in Patients with Cured and Failed Treatment Outcomes. *Front Immunol*. 2017;8. doi:10.3389/fimmu.2017.00690.
- 35•. Malherbe ST, Shenai S, Ronacher K, Loxton AG, Dolganov G, Kriel M et al. Persisting positron emission tomography lesion activity and *Mycobacterium tuberculosis* mRNA after tuberculosis cure. *Nature medicine*. 2016;22(10):1094–100. doi:10.1038/nm.4177. A study demonstrating on-

going pulmonary inflammation at the end of treatment among patients successfully cured for TB disease in South Africa.

36. Lerner TR, Borel S, Gutierrez MG. The innate immune response in human tuberculosis. *Cellular microbiology*. 2015;17(9):1277–85. doi:10.1111/cmi.12480. [PubMed: 26135005]
37. Stutz MD, Clark MP, Doerflinger M, Pellegrini M. Mycobacterium tuberculosis: Rewiring host cell signaling to promote infection. *Journal of leukocyte biology*. 2018;103(2):259–68. doi:10.1002/jlb.4mr0717-277r. [PubMed: 29345343]
38. Wieser V, Moschen AR, Tilg H. Inflammation, cytokines and insulin resistance: a clinical perspective. *Archivum immunologiae et therapiæ experimentalis*. 2013;61(2):119–25. doi:10.1007/s00005-012-0210-1. [PubMed: 23307037]
39. Wellen KE, Hotamisligil GS. Inflammation, stress, and diabetes. *The Journal of clinical investigation*. 2005;115(5):1111–9. doi:10.1172/jci25102. [PubMed: 15864338]
40. de Luca C, Olefsky JM. Inflammation and insulin resistance. *FEBS letters*. 2008;582(1):97–105. doi:10.1016/j.febslet.2007.11.057. [PubMed: 18053812]
41. Bottasso O, Bay ML, Besedovsky H, del Rey A. Immunoendocrine alterations during human tuberculosis as an integrated view of disease pathology. *Neuroimmunomodulation*. 2009;16(2):68–77. doi:10.1159/000180261. [PubMed: 19212126]
42. Besedovsky HO, del Rey A, Klusman I, Furukawa H, Monge Arditi G, Kabiersch A. Cytokines as modulators of the hypothalamus-pituitary-adrenal axis. *The Journal of steroid biochemistry and molecular biology*. 1991;40(4–6):613–8. [PubMed: 1659887]
43. Opolot JO, Theron AJ, Anderson R, Feldman C. Acute phase proteins and stress hormone responses in patients with newly diagnosed active pulmonary tuberculosis. *Lung*. 2015;193(1):13–8. doi:10.1007/s00408-014-9680-8. [PubMed: 25549893] A study that measured hormone responses among patients with TB disease from South Africa.
44. Rey AD, Mahuad CV, Bozza VV, Bogue C, Farroni MA, Bay ML et al. Endocrine and cytokine responses in humans with pulmonary tuberculosis. *Brain, behavior, and immunity*. 2007;21(2):171–9. doi:10.1016/j.bbi.2006.06.005.
45. Bottasso O, Bay ML, Besedovsky H, del Rey A. The immuno-endocrine component in the pathogenesis of tuberculosis. *Scandinavian journal of immunology*. 2007;66(2–3):166–75. doi:10.1111/j.1365-3083.2007.01962.x. [PubMed: 17635794]
46. Kim S-H, Park M-J. Effects of growth hormone on glucose metabolism and insulin resistance in human. *Annals of Pediatric Endocrinology & Metabolism*. 2017;22(3):145–52. doi:10.6065/apem.2017.22.3.145. [PubMed: 29025199]
47. Xiu F, Stanojic M, Diao L, Jeschke MG. Stress hyperglycemia, insulin treatment, and innate immune cells. *Int J Endocrinol*. 2014;2014:486403. doi:10.1155/2014/486403. [PubMed: 24899891]
48. Rubí B, Maechler P. Minireview: New Roles for Peripheral Dopamine on Metabolic Control and Tumor Growth: Let's Seek the Balance. *Endocrinology*. 2010;151(12):5570–81. doi:10.1210/en.2010-0745. [PubMed: 21047943]
49. Li Y, Zhang M, Liu X, Cui W, Rampersad S, Li F et al. Correlates and prevalence of hypogonadism in patients with early- and late-onset type 2 diabetes. *Andrology*. 2017;5(4):739–43. doi:10.1111/andr.12360. [PubMed: 28470687]
50. Li C, Ford ES, Li B, Giles WH, Liu S. Association of testosterone and sex hormone-binding globulin with metabolic syndrome and insulin resistance in men. *Diabetes care*. 2010;33(7):1618–24. doi:10.2337/dc09-1788. [PubMed: 20368409]
51. Kupelian V, Hayes FJ, Link CL, Rosen R, McKinlay JB. Inverse association of testosterone and the metabolic syndrome in men is consistent across race and ethnic groups. *The Journal of clinical endocrinology and metabolism*. 2008;93(9):3403–10. doi:10.1210/jc.2008-0054. [PubMed: 18559915]
52. Floyd K, Glaziou P, Zumla A, Raviglione M. The global tuberculosis epidemic and progress in care, prevention, and research: an overview in year 3 of the End TB era. *The Lancet Respiratory medicine*. 2018;6(4):299–314. doi:10.1016/S2213-2600(18)30057-2. [PubMed: 29595511]
53. Waitt CJ, Squire SB. A systematic review of risk factors for death in adults during and after tuberculosis treatment. *The international journal of tuberculosis and lung disease : the official*

journal of the International Union against Tuberculosis and Lung Disease. 2011;15(7):871–85. doi: 10.5588/ijtld.10.0352.

54. Amere GA, Nayak P, Salindri AD, Venkat Narayan KM, Magee MJ. Contribution of Smoking to Tuberculosis Incidence and Mortality in High Tuberculosis Burden Countries. *American journal of epidemiology*. 2018. doi:10.1093/aje/kwy081.
55. Hannah HA, Miramontes R, Gandhi NR. Sociodemographic and Clinical Risk Factors Associated With Tuberculosis Mortality in the United States, 2009–2013. *Public Health Rep*. 2017;132(3): 366–75. doi:10.1177/0033354917698117. [PubMed: 28394707]
56. Huangfu P, Pearson F, Ugarte-Gil C, Critchley J. Diabetes and poor tuberculosis treatment outcomes: issues and implications in data interpretation and analysis. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease*. 2017;21(12):1214–9. doi:10.5588/ijtld.17.0211.
57. Shewade HD, Jeyashree K, Mahajan P, Shah AN, Kirubakaran R, Rao R et al. Effect of glycemic control and type of diabetes treatment on unsuccessful TB treatment outcomes among people with TB-Diabetes: A systematic review. *PloS one*. 2017;12(10):e0186697. doi:10.1371/journal.pone.0186697. [PubMed: 29059214]
58. Chiang CY, Bai KJ, Lin HH, Chien ST, Lee JJ, Enarson DA et al. The influence of diabetes, glycemic control, and diabetes-related comorbidities on pulmonary tuberculosis. *PloS one*. 2015;10(3):e0121698. doi:10.1371/journal.pone.0121698. [PubMed: 25822974]
59. Jorgensen ME, Faurholt-Jepsen D. Is there an effect of glucose lowering treatment on incidence and prognosis of tuberculosis? A systematic review. *Curr Diab Rep*. 2014;14(7):505. doi:10.1007/s11892-014-0505-1. [PubMed: 24806518]
60. Magee MJ, Bloss E, Shin SS, Contreras C, Huaman HA, Ticona JC et al. Clinical characteristics, drug resistance, and treatment outcomes among tuberculosis patients with diabetes in Peru. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases*. 2013. doi:S1201–9712(13)00050–7 [pii] 10.1016/j.ijid.2012.12.029.
61. Krinsley JS, Egi M, Kiss A, Devendra AN, Schuetz P, Maurer PM et al. Diabetic status and the relation of the three domains of glycemic control to mortality in critically ill patients: an international multicenter cohort study. *Crit Care*. 2013;17(2):R37. doi:10.1186/cc12547. [PubMed: 23452622]
62. Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *The Journal of clinical endocrinology and metabolism*. 2002;87(3):978–82. doi:10.1210/jcem.87.3.8341. [PubMed: 11889147]
63. Investigators N-SS, Finfer S, Chittock DR, Su SY, Blair D, Foster D et al. Intensive versus conventional glucose control in critically ill patients. *The New England journal of medicine*. 2009;360(13):1283–97. doi:10.1056/NEJMoa0810625. [PubMed: 19318384]
64. Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *The New England journal of medicine*. 2008;358(2):125–39. doi:10.1056/NEJMoa070716. [PubMed: 18184958]
65. Fajans SS. I. Identification of chemical diabetes. The definition of chemical diabetes. *Metabolism*. 1973;22(2):211–7. [PubMed: 4631671]
66. Tabarsi P, Baghaei P, Hemmati N, Mirsaedi M, Kazempour M, Mansouri D et al. Comparison of the effectiveness of 2 treatment regimens in patients with isoniazid-resistant tuberculosis. *East Mediterr Health J*. 2009;15(6):1346–50. [PubMed: 20218123]
67. Podell BK, Ackart DF, Obregon-Henao A, Eck SP, Henao-Tamayo M, Richardson M et al. Increased severity of tuberculosis in Guinea pigs with type 2 diabetes: a model of diabetes-tuberculosis comorbidity. *Am J Pathol*. 2014;184(4):1104–18. doi:10.1016/j.ajpath.2013.12.015. [PubMed: 24492198]
68. Podell BK, Ackart DF, Richardson MA, DiLisio JE, Pulford B, Basaraba RJ. A model of type 2 diabetes in the guinea pig using sequential diet-induced glucose intolerance and streptozotocin treatment. *Dis Model Mech*. 2017;10(2):151–62. doi:10.1242/dmm.025593. [PubMed: 28093504]

69. Podell BK, Ackart DF, Kirk NM, Eck SP, Bell C, Basaraba RJ. Non-diabetic hyperglycemia exacerbates disease severity in Mycobacterium tuberculosis infected guinea pigs. *PLoS One*. 2012;7(10):e46824. doi:10.1371/journal.pone.0046824. [PubMed: 23056469]
70. Jawad F, Shera AS, Memon R, Ansari G. Glucose intolerance in pulmonary tuberculosis. *J Pak Med Assoc*. 1995;45(9):237–8. [PubMed: 8683828]
71. Kamper-Jorgensen Z, Carstensen B, Norredam M, Bygbjerg IC, Andersen PH, Jorgensen ME. Diabetes-related tuberculosis in Denmark: effect of ethnicity, diabetes duration and year of diagnosis. *Int J Tuberc Lung Dis*. 2015;19(10):1169–75. doi:10.5588/ijtld.14.0932. [PubMed: 26459528]
72. Pearson F, Huangfu P, Pearce M, McNally R, Unwin N, Critchley JA. Exploring the association between tuberculosis and diabetes in a UK primary care dataset. Society for Social Medicine, 60th Annual Scientific Meeting; 14–16 September 2016; University of York: *Journal of Epidemiology & Community Health*; 2016.
73. Salindri AD, Wang JY, Wang CH, Wu CY, Lin HH, Magee MJ. Risk factors for incident diabetes among a cohort of patients previously treated for tuberculosis in Taiwan. 2017.
74. Baghaei P, Marjani M, Javanmard P, Tabarsi P, Masjedi MR. Diabetes mellitus and tuberculosis facts and controversies. *Journal of diabetes and metabolic disorders*. 2013;12(1):58. doi:10.1186/2251-6581-12-58. [PubMed: 24360398]
75. Ali Abdelhamid Y, Kar P, Finnis ME, Phillips LK, Plummer MP, Shaw JE et al. Stress hyperglycaemia in critically ill patients and the subsequent risk of diabetes: a systematic review and meta-analysis. *Crit Care*. 2016;20(1):301. doi:10.1186/s13054-016-1471-6. [PubMed: 27677709] A review that reported stress hyperglycemia during hospitalization is associated with increased risk of incident diabetes after discharge.
76. Alisjahbana B, Sahiratmadja E, Nelwan EJ, Purwa AM, Ahmad Y, Ottenhoff THM et al. The Effect of Type 2 Diabetes Mellitus on the Presentation and Treatment Response of Pulmonary Tuberculosis. *Clin Infect Dis*. 2007;45(4):428–35. doi:10.1086/519841. [PubMed: 17638189]
77. Faurholt-Jepsen D, Range N, PrayGod G, Jeremiah K, Faurholt-Jepsen M, Aabye MG et al. The role of diabetes on the clinical manifestations of pulmonary tuberculosis. *Tropical Medicine & International Health*. 2012;17(7):877–83. doi:10.1111/j.1365-3156.2012.03002.x. [PubMed: 22574967]
78. Restrepo BI, Fisher-Hoch SP, Crespo JG, Whitney E, Perez A, Smith B et al. Type 2 diabetes and tuberculosis in a dynamic bi-national border population. *Epidemiol Infect*. 2007;135(3):483–91. doi:10.1017/S0950268806006935. [PubMed: 16863600]
79. Critchley JA, Restrepo BI, Ronacher K, Kapur A, Bremer AA, Schlesinger LS et al. Defining a Research Agenda to Address the Converging Epidemics of Tuberculosis and Diabetes: Part 1: Epidemiology and Clinical Management. *Chest*. 2017;152(1):165–73. doi:10.1016/j.chest.2017.04.155. [PubMed: 28434936]
80. El-Osta A, Brasacchio D, Yao D, Poci A, Jones PL, Roeder RG et al. Transient high glucose causes persistent epigenetic changes and altered gene expression during subsequent normoglycemia. *J Exp Med*. 2008;205(10):2409–17. doi:10.1084/jem.20081188. [PubMed: 18809715]
81. Jayaraman S Epigenetic mechanisms of metabolic memory in diabetes. *Circ Res*. 2012;110(8):1039–41. doi:10.1161/CIRCRESAHA.112.268375. [PubMed: 22499895]
82. Fernandez-Morera JL, Rodriguez-Rodero S, Menendez-Torre E, Fraga MF. The possible role of epigenetics in gestational diabetes: cause, consequence, or both. *Obstet Gynecol Int*. 2010;2010:605163. doi:10.1155/2010/605163. [PubMed: 21052542]
83. Bouchard L, Thibault S, Guay SP, Santure M, Monpetit A, St-Pierre J et al. Leptin gene epigenetic adaptation to impaired glucose metabolism during pregnancy. *Diabetes care*. 2010;33(11):2436–41. doi:10.2337/dc10-1024. [PubMed: 20724651]
84. Bandaru P, Shankar A. Association Between Plasma Leptin Levels and Diabetes Mellitus. *Metab Syndr Relat D*. 2011;9(1):19–23. doi:10.1089/met.2010.0037.
85. Nathan DM, Cleary PA, Backlund JYC, Genuth SM, Lachin JM, Orchard TJ et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *New England Journal of Medicine*. 2005;353(25):2643–53. [PubMed: 16371630]

86. Yessoufou A, Moutairou K. Maternal diabetes in pregnancy: early and long-term outcomes on the offspring and the concept of “metabolic memory”. *Exp Diabetes Res.* 2011;2011:218598. doi: 10.1155/2011/218598. [PubMed: 22144985]
87. WorldHealthOrganization. Global Tuberculosis Report 2017 Geneva: World Health Organization 2017.
88. Li L, Lin Y, Mi F, Tan S, Liang B, Guo C et al. Screening of patients with tuberculosis for diabetes mellitus in China. *Tropical medicine & international health : TM & IH.* 2012;17(10):1294–301. doi:10.1111/j.1365-3156.2012.03068.x. [PubMed: 22830945]
89. Duangrithi D, Thanachartwet V, Desakorn V, Jitruckthai P, Phojanamongkolkij K, Rienthong S et al. Impact of diabetes mellitus on clinical parameters and treatment outcomes of newly diagnosed pulmonary tuberculosis patients in Thailand. *Int J Clin Pract.* 2013;67(11):1199–209. doi:10.1111/ijcp.12215. [PubMed: 23750554]
90. Almeida-Junior JL, Gil-Santana L, Oliveira CA, Castro S, Cafezeiro AS, Daltro C et al. Glucose Metabolism Disorder Is Associated with Pulmonary Tuberculosis in Individuals with Respiratory Symptoms from Brazil. *PloS one.* 2016;11(4):e0153590. doi:10.1371/journal.pone.0153590. [PubMed: 27078026]
91. Tahir Z, Ahmad MU, Akhtar AM, Yaqub T, Mushtaq MH, Javed H. Diabetes mellitus among tuberculosis patients: a cross sectional study from Pakistan. *Afr Health Sci.* 2016;16(3):671–6. doi: 10.4314/ahs.v16i3.5. [PubMed: 27917198]
92. Workneh MH, Bjune GA, Yimer SA. Prevalence and Associated Factors of Diabetes Mellitus among Tuberculosis Patients in South-Eastern Amhara Region, Ethiopia: A Cross Sectional Study. *PloS one.* 2016;11(1):e0147621. doi:10.1371/journal.pone.0147621. [PubMed: 26808967]
93. Abdelbary BE, Garcia-Viveros M, Ramirez-Oropesa H, Rahbar MH, Restrepo BI. Tuberculosis-diabetes epidemiology in the border and non-border regions of Tamaulipas, Mexico. *Tuberculosis.* 2016;101S:S124–S34. doi:10.1016/j.tube.2016.09.024. [PubMed: 27733244]
94. Lee EH, Lee JM, Kang YA, Leem AY, Kim EY, Jung JY et al. Prevalence and Impact of Diabetes Mellitus Among Patients with Active Pulmonary Tuberculosis in South Korea. *Lung.* 2017;195(2): 209–15. doi:10.1007/s00408-017-9978-4. [PubMed: 28184994]
95. Mave V, Meshram S, Lokhande R, Kadam D, Dharmshale S, Bharadwaj R et al. Prevalence of dysglycemia and clinical presentation of pulmonary tuberculosis in Western India. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease.* 2017;21(12):1280–7. doi:10.5588/ijtld.17.0474.

Figure 1.

Metabolic and endocrine changes during tuberculosis disease that theoretically contribute to stress hyperglycemia. Pro-inflammatory and anti-inflammatory cytokines released during active tuberculosis disease stimulate increase production of cortisol, ACTH, prolactin and growth hormone which increase gluconeogenesis and glycolysis in liver and kidney, increase insulin resistance and decrease glucose uptake resulting in increased blood sugar level. Cytokines can also act on hypothalamus-pituitary-gonadal axis resulting in lower DHEA and testosterone level leading to increase insulin resistance followed by hyperglycemia. Cytokines, nitric oxide and reactive oxygen species also increase insulin resistance and

hyperglycemia. IL: Interleukin; TNF: tumor necrosis factor; ACTH: adrenocorticotrophic hormone; T3 & T4: thyroid hormones; DHEA: dehydroepiandrosterone.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 1.

Proportion of patients with tuberculosis-diabetes comorbidity that are newly diagnosed with diabetes during tuberculosis treatment, observational studies 2012–2018

Study (Year)	Setting	Patients with TB & newly diagnosed diabetes (N)	All patients with TB and diabetes (N)	Proportion (%) newly diagnosed with diabetes (95% CI)
Li et al. (2012)[88]	China	227	1090	21 (18–23)
Duangrithi et al. (2013)[89]	Thailand	11	37	30 (15–44)
Magee (2015)[25]	Georgia	9	37	24 (10–38)
Almacida et al. (2016)[90]	Brazil	25	44	57 (42–71)
B-Blanco et al. (2016)[18]	Tanzania	33	38	87 (76–98)
Tahir et al. (2016)[91]	Pakistan	52	74	70 (60–81)
Workneh et al. (2016)[92]	Ethiopia	64	109	59 (49–68)
Kornfeld et al. (2016)[20]	India	37	113	33 (24–41)
Abdelbary (2016)[93]	Mexico	350	2121	17 (15–18)
Aftab et al. (2017)[17]	Pakistan	408	1200	34 (31–37)
Lee et al. (2017)[94]	S Korea	20	253	8 (5–11)
Mave et al. (2017)[95]	India	66	162	41 (33–48)
Weighted Average				22 (21–23)

CI: confidence interval