Tuberculosis and diabetes mellitus: Relating immune impact of co-morbidity with challenges in disease management in high burden countries

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ABSTRACT
Mycobacterium tuberculosis (MTB) is the causative agent of TB. TB incidence is high in many low resource settings where limited health systems make it difficult for screening of co-morbid conditions. Susceptibility to TB is increased with coincident diabetes mellitus (DM) or prediabetes. DM leads to chronic, subclinical inflammation in the host leading to compromised protective immunity against MTB, impacting TB treatment. This review focuses on the immunological impact of DM and prediabetes on TB infections, highlighting the importance of having effective diagnostic, treatment and management programs for early identification of hyperglycemia in TB patients to improve treatment outcomes. Further, it describes challenges in monitoring of TB and DM co-morbidity in a high-burden setting.

1. Introduction
Tuberculosis (TB) is a disease caused by Mycobacterium tuberculosis (MTB) that primarily affects the lungs. In 2020, TB caused an estimated 1.5 million deaths and an incidence of 10 million cases worldwide [1]. TB has been on the rise since the 1980s, in part due to the HIV pandemic, growing multidrug resistance in MTB, and also increased numbers of highly susceptible individuals such as, those with Type 2 Diabetes mellitus (DM) [2]. Currently, one-quarter of the population of the world is latently infected with MTB [3]. Individuals with latent tuberculosis infection (LTBI) are not infectious but may subsequently develop active TB due to reactivation of infection. This can occur as a consequence of granuloma liquefaction particularly in immune deficient or immuno-compromised individuals, such as individuals with HIV or DM [4]. Individuals with DM and pre-diabetes (PDM) have been shown to suffer from chronic, sub-clinical inflammation that impacts effective immune function. Those with DM and PDM are more susceptible to TB infection than non-diabetics. Here we describe how DM- and PDM-related inflammation leads to increased susceptibility to TB. Further, here we address the need for optimally managing DM in patients with TB.

2. Burden of TB-DM in Asian countries
The WHO TB report for 2020 published on 14th October 2021, identified TB as 13th leading cause of death worldwide, with estimated 10 million new cases and 1.5 million deaths. Among the new cases reported, 88 % were those from high TB burden countries among which India lead the count, followed by China, Indonesia, Philippines, Pakistan, Nigeria, Bangladesh and South Africa [1]. The South Asian region consists of eight low and middle-income nations, namely Afghanistan, Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan, and Sri Lanka. They account for nearly 44 % of world TB cases and a high burden of TB mortality (681,975 deaths), 38 % of the worldwide burden [5].

The burden of cardio-metabolic diseases, particularly diabetes (DM) has become a major health problem in South Asian countries, with an expected rise in prevalence of DM of more than 151 % between 2000 and 2020 [6]. Moreover, population of this region is at higher risk of

Abbreviations: DM, type-2 diabetes mellitus; MTB, Mycobacterium tuberculosis; TB, tuberculosis.
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developing DM as compared to other ethnic groups [7]. Prevalence of DM in active TB cases is also on rise globally and especially, in South Asia since 2000 [8]. DM is found to escalate the risk of contracting TB by three folds [9]. In 2009, the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease (IUATLD) have recommended bi-directional TB-DM screening and integrated management for both diseases in high burden countries [10].

A systemic review and meta-analysis of 74 studies (47 studies from India, 10 from Pakistan, four from Nepal and two from both Bangladesh and Sri-Lanka), showed the pooled prevalence of DM in TB patients to be 21%, varying from 11% in Bangladesh to 24% in Sri-Lanka [11]. Prevalence of DM in active TB cases is also on rise in South Asia since 2000 [8]. With an estimated 510000 new TB cases emerging each year, approximately 15,000 are reported to develop drug resistant TB every year. Pakistan is ranked fifth among TB high-burden countries worldwide and it accounts for 61% of the TB burden in the WHO Eastern Mediterranean Region [12]. Pakistan has a high burden of DM as well as TB. Type 2 DM is 16.98% prevalent [13]. Different studies have reported a high rate of TB and DM co-morbidity in Pakistan. In one study, it was found after screening of 211 TB patients, 11.4% were diabetic while 21.3% were found to be PDM [14]. A prospective cohort study on the prevalence of DM in pulmonary TB patients revealed 18% of TB patients were diabetic and were more likely to have unfavorable outcomes as compared to non-diabetic pulmonary TB patients [15]. Through bi-directional screening, it was also found that 13.5% of cases with TB had newly diagnosed DM and 26.1% were already known cases of TB-DM, contributing to an overall 39.6% prevalence of DM among TB patients [16]. Diabetes was also found to cause more of multi-drug resistant tuberculosis (MDR-TB) as compared to non-diabetic Pakistani population [17].

3. The impact of diabetes and pre-diabetes on host immunity

DM is a complex and multi factorial disease which is caused either by insufficient production of insulin or insulin resistance by the cells or both [18]. DM is characterised primarily by (postprandial and post-absorptive) hyperglycaemia, impaired secretion of insulin (by pancreatic β-cells); and insulin resistance. Insulin resistance, the failure of a known quantity of insulin to stimulate the uptake of glucose in the body, can develop as a result of multiple factors such as, genetic abnormalities in one or more proteins belonging to the insulin action cascade, foetal malnutrition, and/or a rise in visceral adiposity [19]. In the context of insulin resistance, the liver is no longer able to suppress the release of glucose into the blood resulting in hyperglycaemia. Tissues in which insulin resistance typically occurs include the muscles, liver, and fat. The global burden of DM was found to be close to 500 million in 2017, with a predicted rise of 7079 per 100,000 population by 2030 [20].

PDM is a high-risk state for progression to DM. PDM have blood glucose levels elevated above the normo-glycaemic range but maintained below the threshold for DM. Unlike DM, PDM typically has no overt signs or symptoms other than impaired fasting glucose and/or impaired glucose tolerance [21]. The prevalence of PDM is on the rise globally, it is estimated that over 470 million people will have PDM by 2030 [22].

Uncontrolled DM can lead to alterations in the immune system, increasing the risk of susceptibility to infections including that with MTB. Chronic sub-clinical inflammation is an important hallmark of DM [23], and studies suggest that it is a component of the pre-diabetic state, as well [24]. Inflammation plays an important role in the aetiology of DM, although the exact mechanisms through which it promotes pathogenesis are unclear. However, systemic, low-grade inflammation throughout the body is considered to be conducive to the development of PDM and DM due to the ability of inflammation to induce organ dysfunction [25], leading to hyperglycaemia and insulin resistance. It remains unclear whether this inflammation always arises as a result of hyperglycaemia and/or insulin resistance, or vice versa. Altered immune responses could be attributed to factors such as the elevated glucose concentration, leading to the production of Advanced Glycation End products (AGE) and the constant inflammation, associated with DM. DM is considered, by some, not solely a metabolic disease but a disease of the immune system [26].

4. Inflammation in control of TB

Inflammation is a protective host response aimed at defending against invading pathogens. In response to MTB infection, an intricate network of cytokines is established by cells of the innate and adaptive immune systems, directly or indirectly triggering anti-mycobacterial responses [27]. In the early phase of defence, cells such as alveolar macrophage (AM), dendritic cells (DCs), neutrophils, monocytes and natural killer (NK) cells secrete pro-inflammatory cytokines in order to attract additional leukocytes to the site of infection for further support against MTB [28]. This is followed by the emergence of the adaptive immune response, driven largely by CD4+ and cytotoxic CD8+ T-lymphocytes [29]. Together, these cell populations, each expressing distinct pro- and/or anti-inflammatory cytokine profiles, elicit diverse cellular responses all directed towards restricting the growth of MTB and eliminating the reservoir of infection.

Of the pro-inflammatory cytokines, IFN-γ is absolutely crucial for the control of MTB. Secreted primarily by CD4+ and CD8+ lymphocytes, as well as NK cells [30], it elicits a range of complex cellular responses to MTB from a variety of cell types. Its principle role is to activate the innate bactericidal properties possessed by macrophage. TNF-α is another powerful pro-inflammatory cytokine secreted primarily by macrophage and Th1 (CD4+) cells, working synergistically with IFN-γ to boost intracellular killing of phagocytised mycobacteria [29]. Its role extends to controlling the maintenance of the granuloma, rendering TNF-α critical for the containment of persistent TB.

Optimal functioning of the required defence responses are dependent on the network and relative abundance of cytokines induced at varying stages of infection. Inadequate inflammation, through overexpression of anti-inflammatory cytokines or under-expression of pro-inflammatory cytokines, results in failure to clear infection and widely disseminated disease [31,32]. For example, in the absence of IFN-γ, the intracellular environment of the macrophage remains at a neutral pH, with diminished reactive radical production, and phagolysosomal fusion does not take place resulting in failure to kill intracellular MTB [33]. Diminished quantities of TNF-α are associated with mortality, attributed in part to the weakened anti-mycobacterial action of macrophage in addition to impaired control of the granuloma [34]. Inhibition of TNF-α (reduced inflammation) leads to acute, disseminated disease, and allows for reactivation of LTBi in animal models [35]. The pro-inflammatory cytokine profiles in TB patients is found to vary across the disease spectrum, increasing from minimal to severe disease for IFN-γ, CXCL9 and other Type-I cytokines [36]. However, although pro-inflammatory cytokines are intended to impart protection against MTB infection, excessive inflammation compromises the functionality of the innate and adaptive immune systems and promotes immunopathology. Regulation of IFN-γ is required for MTB control and this is affected by suppressor of cytokine signalling (SOCS) 1 molecules which, are shown to be upregulated in TB infections [37].

The interactions between the myriad of cytokines secreted during different phases of infection, and how these cytokines influence the host cell and MTB have significant implications for the clinical outcome of infection (whether infection is cleared, remains latent or progresses to active disease) [28]. It is crucial that levels of pro- and anti-inflammatory cytokines are maintained at levels optimal for promoting anti-mycobacterial action and minimising damage to host tissues.

5. Prediabetes and TB

There have been a limited number of studies focusing on
incorporating the analysis of subjects with PDM with regard to TB. High prevalence of PDM amongst those with, or at risk of, TB has also been reported in recent studies [38–39]. PDM is also independently associated with active TB [40]. Due to certain shared characteristics (hyperglycaemia and at times insulin resistance) between the two conditions, it has been speculated that DM and PDM may share similar pathologies with regard to aberrant immune responses. The few studies on this topic have investigated the cytokine profiles of PDM-TB individuals presenting conflicting evidence. In one study, circulating levels of IFN-γ, TNF-α and IL-2 (type 1), IL-17A and IL-17F (type 17), and IL-1p, IFNβ and GM-CSF (pro-inflammatory) cytokines were found to be elevated in TB-PDM individuals, as were systemic levels of the IL-5 (type 2), IL-10 and TGFβ (regulatory) cytokines. These findings suggest that PDM is not associated with an imbalance of pro- and anti-inflammatory cytokines but rather with their overall heightened expression in response to active TB infection in comparison to TB patients without PDM [41]. In contrast, the presence of PDM in individuals with coincident LTBi (PDM-LTBi) was found to drastically reduce circulating plasma levels of IFN-γ, TNF-α, IL-2, IL-17F, and systemic levels of IL-1p, IL-18 (pro-inflammatory) and IL-10 (anti-inflammatory) at homeostasis, in comparison to individuals with only LTBi in another recent study [42].

6. Impact of tuberculosis and diabetes mellitus on host immunity

The function of neutrophils, macrophages, Natural Killer (NK) cells, and some other components of innate immunity is drastically compromised by metabolic alterations in DM [43]. Alveolar macrophages have a central role in hosts for MTB infection and replication, these macrophages ingest the bacilli to enclose them in phagosomes and fuse with lysosome along with digestion of the bacteria and production of antimicrobial molecules like reactive nitrogen intermediates which leads to formation of “granulomas,” which contain other immune effector cells, such as neutrophils and T cell [44].

Dysregulation of the immune system is a well-established feature of DM, characterised in part by impaired cytokine secretion [45]. DM is known to increase the risk of MTB infection in individuals, diabetics are more susceptible to both developing active TB [46] or the reactivation of latent TB [47] in comparison to non-diabetics.

Alveolar macrophages from diabetic mice had increased the expression of CCR2, which may restrain monocyte traffic to the lung, and reduced expression of CD14 and macrophage receptor which recognizes the MTB cell wall components that contribute to reduced phagocytosis of MTB and increase tuberculosis susceptibility in diabetic hosts [44].

Adaptive immunity against MTB infection is mostly cellular immune responses [48]. T helper 1 (Th1) cells play a central role in the host defense by inducing the production of IFNγ, which potentiates the nitric oxide-(NO-) dependent killing activity of macrophages, while IL-2 is an essential cytokine for the development and proliferation of Th1 and CD8+ T cells, and Th17 cell secretes IL-17 and IL-23 that plays inflammatory response of TB [49].

With regard to the immune response to TB in DM patients, data suggest that TB-DM is characterised by a pro-inflammatory milieu. One study revealed that circulating levels of IFN-γ, TNF-α, IL-2 (type 1), IL-5 (type 2) and IL-17A (type 17) cytokines, as well as systemic levels of additional pro-inflammatory cytokines such as IL-1β, IL-6 and IL-18, are raised at baseline in patients with coincident DM and pulmonary TB [50]. Furthermore, plasma levels of type 1 and type 17 cytokines were positively correlated with HbA1c levels of DM patients, suggesting that poor glycaemic control contributes to the pro-inflammatory environment observed amongst DM patients [50]. Further work also describes heightened pro-inflammatory responses in TB-DM patients following exposure of whole-blood to MTB antigens, in comparison to TB patients without DM [50].

Frequencies of mono- and dual-functional (producing one or two cytokines) (IFN-γ, TNF-α or IL-2) CD4+. Th1 cells are also increased following exposure to MTB antigens in DM patients [51]. Overall, these findings indicate an elevation of pro-inflammatory cytokine levels as well as heightened Th1 and Th17 cell and cytokine responses in TB-DM patients.

MTB infection with diabetes can be rapidly progressive with a shortened survival interval and more severe pulmonary and extra pulmonary pathologies [52]. The higher bacterial burden observed as compared to non-DM controls is associated with increased disease severity, miliary TB, and higher bacterial load that contribute to increased mortality rates of TB-DM patients [52].

It has also been reported that patients with PTB and concomitant DM were more likely to present with hemoptysis, positive acid-fast bacilli (AFB) smear, cavity, higher erythrocyte sedimentation rate (ESR), higher serum C-reactive protein (CRP), lower serum albumin (ALB), or higher fasting blood glucose (FBG), as compared to non-diabetics [53].

Individuals with TB and DM comorbidity have been shown to have heightened levels of pro-inflammatory cytokines both prior to ATT, and during the course of TB treatment [54]. This has clinical significance as excessive and prolonged inflammation results in increased morbidity and mortality in pulmonary TB largely, as a consequence of immune-mediated lung damage [54].

Overall, aberrant functioning of the immune system in DM may predispose DM patients to infectious diseases which require strong cell-mediated immune responses. Further studies are required to elucidate the impact of diabetes-related inflammation on the immune response to MTB, and whether it exacerbates cellular responses that promote immune-mediated pathology during the course of MTB infections.

7. Impact of DM on treatment outcomes in TB

DM has been observed to negatively influence treatment outcomes for patients with coincident TB. Uncontrolled DM either due to internal and external factors, worsens disease outcomes. This may be attributable to various factors, such as immune dysregulation in the form of impaired monocyte chemotaxis, diminished production of Th1-pattern cytokines and nitric oxide [55] and elevated innate and type 1 cytokine expression [40]. The clinical presentation of TB is also more complex in patients with DM. Patients present with more cavitary disease, higher severity and atypical sites like lower lobe predominance [56]. TB patients with DM are found to have higher bacillary loads as compared to non-diabetics, resulting in more smear or culture positivity and a delayed mycobacterial clearance [57]. Indicators for successful TB treatment are slowed down in patients with DM in comparison to non-diabetics such as sputum culture conversion. Several studies show that sputum culture conversion, from positive to negative, is delayed in DM patients [57]. Research also shows that DM patients are at significantly higher risk of relapse after completion of TB treatment [58]. Additional negative treatment outcomes include slower improvement of pulmonary lesions following treatment, higher likelihood of recurring infection, and increased probability of treatment failure and death in DM patients [58]. TB with DM has also been associated with an increased risk of cardiovascular complications such as, myocardial infarction and stroke during the early months of TB treatment in patients [59].

8. Factors affecting TB-DM treatment:

TB treatments are the same in patients regardless of their diabetes status. However, as DM is associated with a slower treatment response, increased drug resistance, treatment failures and relapsed TB, the duration of ATT may need to be prolonged to prevent poor outcome. A study from Taiwan showed a lower relapse rate and better treatment outcomes with a nine-month as compared with a six-month treatment regimen (hazard ratio 0.76; 95 % CI 0.59–0.97) [60]. A large meta-analysis of 13 studies found a significant association between diabetes and MDR TB (OR 1.71, 95 % CI 1.32–2.22) [61]. In another meta-analysis including 24 observational studies, a higher rates of MDR-TB
(OR = 1.97, 95 % CI = 1.58–2.45) was found in diabetics, irrespective of country income level [62]. Possible reasons of acquiring drug-resistance were higher initial bacterial load and slower response to treatment [63]. Drug susceptibility should be done in TB–DM patients both at baseline and during follow-up to identify drug resistance and poor outcome. Further, TB–DM patients may experience more side-effects and drug-toxicity and drug interactions during TB treatment need a close follow-up in these patients. Factors that impact DM and therefore treatment outcomes in TB are discussed below.

8.1. Poor glycemic control

Achieving optimum glycaemic control is important but can be very difficult due to scarcity of adequate health care facilities, low educational status, and economic disparities in TB patients. A 5-year survey, documenting changes in diabetes practice in developing regions that included 11,799 patients showed that only 20–30 % of patients were at the HbA1c < 7 % goal [64]. Poor glycaemic control in Asian populations represents a potentially important risk factor for TB. The Diabcare-Asia project, a cross-sectional survey of 24,317 diabetic patients from Bangladesh, China, India, Indonesia, Malaysia, Pakistan, Philippines, Singapore, South Korea, Sri Lanka, Taiwan, Thailand, and Vietnam, found that 55 % of patients had values of HbA1c exceeding 8 % [65]. A study showed that poor DM control (as indicated by HbA1c level) was associated with differences in the innate and cellular cytokine responses to stimulation with purified protein derivative from MTB, thus facilitating progression to active TB [66]. A study of 4,690 elderly diabetic patients in Hong Kong, showed that the patients with greater HbA1c value (>7%) with a hazard risk of active TB that was 3 times increased compared with those who had HbA1c < 7 % (HR 3.11, 95 % CI 1.63–5.92, p < 0.01) [67]. A cohort study with 123,546 individuals performed in Taiwan found that, during a median follow-up period of 4.6 years, diabetic patients with poor glycaemic control had a significantly higher hazard risk of TB (adjusted HR 2.21; 95 % CI 1.63–2.99, p < 0.01) compared to those without DM [68]. The evidence of poor glycaemic control in Asian patients, along with the fact that poor glycaemic control represents an important risk factor for TB, call for further therapeutic actions in order to decrease TB–DM prevalence in developing Asian countries.

8.2. Insulin resistance

Chao et al. investigated the immunological mechanisms underlying the susceptibility of diabetic patients to TB [69]. They measured the level of resistin, a protein produced by immune cells in humans that causes insulin resistance and inhibits reactive oxygen species (ROS) production in leukocytes, and found that serum resistin levels were significantly higher in patient groups with severe TB and DM when compared with mild TB cases and healthy controls. They hypothesized that functional changes in macrophages seen in the state of insulin resistance may increase the risk for active TB [69].

8.3. Genetic make-up

Compared with European populations, Asians tend to develop diabetes at a younger age and at much higher incidence rates given the same amount of weight gain. Genome-wide association studies (GWAS) have identified over 70 loci associated with DM. Although the majority of GWAS results were conducted in populations of European ancestry, recent GWAS in Asians have made important contributions to the identification of DM susceptibility loci, which suggest the different genetic make up of Asian population in its diabetic patients [70]. It is striking that even when they are not in their home countries, people of Asian or Indian/subcontinental origin show a higher prevalence of DM in the presence of TB than the rest of the population. A study comprising of four ethnicities found the group most affected from both diseases (TB–DM) was that of patients of subcontinental and Asian origin (55 %) [71]. Black and white populations were affected in almost equal proportions (22 % and 23 %) with the conclusion that about one-third of Asians with newly diagnosed TB will have DM [71].

8.4. Gender and age

A higher prevalence of TB and TB–DM in males as compared to females was shown in Brazil [72]. Globally, 12 % of TB cases accounts for children and adolescence [73]. A high prevalence of TB–DM comorbidity in Asian countries, especially in China and India, may be a result of the rapidly increasing prevalence of young-onset DM in these countries. In southern India, from 2000 to 2006, the prevalence of DM in people younger than 44 years increased by 10.7 %. Data from China also showed an 88 % increase in the prevalence of maturity-onset DM in the 35–44 years age group, probably due to the rapid transition in dietary habits, reduced physical activity, longer working hours, and decreasing sleep hours. Although the data is very ambiguous, it has been shown that the relation between DM and TB is more prominent in younger people [74] and this might be due to onset of diabetes in early age. However some data suggest, sex, older age, poor glycemic control, having family history of DM and TB illness are among the variables identified as associated risk factors for TB–DM comorbidity [75]. A study reports higher lung damage in TB–DM as compared to TB alone in older population with a dominance of 50–60 years of age groups [76].

9. Challenges in screening for diabetes in TB patients.

Early identification of diabetes requires improvement at the level of health systems. Often patients are unaware that they have raised glycemcic levels. This has been demonstrated by reports from Pakistan which showed that of newly diagnosed TB patients, 11.4 % patients had diabetes and 21.3 % had prediabetes whilst further, 71 % of the diabetics in the group studied did not know their hyperglycemic status [77]. Health care providers in the private sector also need to be cognizant of underlying diabetes which may impact treatment outcome. Access to blood glucose testing is a limitation. Point of care glucometer testing needs to be available at TB screening centers. Further, upon diagnosis of diabetes it is essential that patients are guided to diabetic management services, counselling is required to guide patients regarding diet, lifestyle and also treatment that may need to be taken. In systems where patients pay out of pocket, identification of diabetes does not directly lead to immediate management of the conditions. Medications are costly and may require multiple adjustments in dosage and regimen to reach appropriate levels for individual cases. It is the health-seeking behavior which needs to be modified in order to have a full impact on DM management generally and also in the context of TB–DM. Further, TB medications (especially rifampicin and isoniazid) interact with those used to control blood sugars resulting in sub-optimal control of hyperglycemia [78] and underlying DM needs to be differentiated from treatment induced condition. Overall, it is a holistic approach to TB and DM management that can benefit patients as neither condition can be treated separately.

10. The way forward

Whilst TB and DM screening has been recommended by the World Health Organization STOP TB initiatives as part of the End-TB strategy, screening is not always practiced [79]. There need to be an increasing awareness raising and implementation of DM screening and management at the level of National TB Control Programs. Efforts are underway through Universal Health Coverage (UHC) initiative. However, implementation of the programs and impact on outcomes need to be closely monitored.

One option would be to integrate care of non-communicable diseases (NCDs) like DM with common communicable diseases at primary
healthcare facilities. Holistic, patient-centered care would improve screening of diabetic patients for latent or active TB and that of TB patients, for concomitant glucose intolerance or DM.

11. Conclusions

There is strong evidence for the association between dysregulation of glycemic control and susceptibility to MTB infection. Given the impact of TB and DM comorbidity on treatment and management of the disease, it is particularly important for public health measures to be put in place for early diagnosis and management of DM. Often, pre-diabetes is not identified as a health risk, however it is a potentially manageable condition which can be improved with lifestyle modifications. It is important that blood sugar levels be monitored in DM and in those with TB and DM co-infection and, this is particularly important. Adaptation of TB treatment protocols in patients with DM may lead to reduction in morbidity, glycemic control and better TB outcomes. This will help lead towards End-TB Strategy and Sustainable Development Goals for TB elimination.

Authorship statement

ZH designed and supervised the review. UA and AK prepared the first draft. MI, NS and BJ discussed management of TB cases. UA, KIM, MI and ZH finalised the manuscript. All authors approved the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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