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Article

Diabetes-associated Susceptibility to Tuberculosis: Contribution of Hyperglycemia vs. Dyslipidemia

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Abstract: Diabetes is a major risk factor for tuberculosis (TB). Diabetes increases the risk of progression from latent tuberculosis infection (LTBI) to active pulmonary TB and TB patients with diabetes are at greater risk of more severe disease and adverse TB treatment outcomes compared to TB patients without co-morbidities. Diabetes is a complex disease characterized not only by hyperglycemia but also various forms of dyslipidemia. However, the relative contribution of these underlying metabolic factors to increased susceptibility to TB are poorly understood. This review summarizes our current knowledge on epidemiology and clinical manifestation of TB and diabetes comorbidity. We subsequently dissect the relative contribution of body mass index, hyperglycemia, elevated cholesterol and triglycerides on TB disease severity and treatment outcomes. Lastly, we discuss the impact of selected glucose and cholesterol lowering treatments frequently used in the management of diabetes on TB treatment outcomes.

Keywords: Tuberculosis, Mycobacterium tuberculosis, diabetes, hyperglycemia, dyslipidemia, cholesterol, triglycerides

1. Introduction

Approximately 2 billion people world-wide are estimated to be infected with *Mycobacterium tuberculosis* (Mtb) [1]. Of those 5-10% will develop active tuberculosis (TB) in their lifetime. In 2019, 10 million people suffered from active TB, which caused 1.5 million deaths [2]. The cost for TB prevention, diagnosis and treatment is expected to double from 6.5 billion USD in 2020 to 13 billion USD per year by 2022. This highlights that TB remains a global health threat and a significant financial burden. The proposed 2020 milestone of a 20% reduction in TB cases, and 35% reduction in deaths between 2015-2020 was not reached, although global TB incidence rates and annual death numbers are decreasing [2]. The goal to achieve an 80% decrease in TB incidence or 90% decrease in annual death by 2030 will not be met without intensified effort. Several factors including malnutrition, diabetes, smoking, and alcohol abuse contribute to an increase in susceptibility to TB. With the rapid rise in type 2 diabetes (T2D) prevalence in developing countries a significant risk factor for TB is emerging. T2D affects one in 11 individuals globally (463 million people), and almost 50% of T2D patients are undiagnosed [3]. It is projected that the number of T2D patients will increase by 51% reaching 700 million people in 2045 [3], with most cases living in developing countries, where TB is endemic [4]. Hence, an increase in the global burden of T2D-TB comorbidity is expected in the next decade.

The COVID 19 pandemic has adversely affected the global efforts to control both TB and T2D, especially in low- and middle-income countries. According to a WHO statement made from surveys of 163 countries, 49% of the surveyed countries have seen access reduced to the treatment of T2D [5]. Globally, if the number of new TB cases detected over a 3-month period during the pandemic reduces by 25% compared to the level of detection prior to the pandemic, an additional 190,000 TB deaths are estimated [6]. It is inevitable

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that the pressures on the healthcare systems by the COVID-19 pandemic around the world, will likely result in a delay in the fight against both TB and T2D.

This review article discusses the current knowledge of the association between TB and T2D with particular focus on the contribution of metabolic factors including body mass index (BMI), hyperglycemia and dyslipidemias to increased susceptibility to TB.

2. Impact of T2D on latent TB infection and active TB disease

2.1 T2D increases the risk of latent TB infection

Latent TB infection (LTBI), defined as asymptomatic infection with Mtb, usually precedes active pulmonary TB. Studies assessing the association between T2D and LTBI are most valuable if conducted in low TB burden countries as baseline LTBI positivity is high irrespective of T2D status in high TB burden countries like South Africa [7]. In a cross-sectional study conducted in a health clinic in Atlanta, GA, USA, LTBI was significantly higher amongst patients with T2D (43.4%) and pre-diabetes (39.1%) compared to those without T2D (25.9%). Further, a strong association between T2D and LTBI ([aOR] 2.3, 95% CI 1.2–4.5) was demonstrated in this cohort of patients [8]. This relationship between TB and LTBI was also identified by Lee et al., who found T2D to be associated with a small but significantly increased risk of LTBI (pooled OR of 1.18, 95%CI 1.06–1.30) [9]. In a large-cross sectional analysis using US National data, Barron et al., reported a significantly higher association of T2D and LTBI (aOR 1.90, 95%CI 1.15–3.14) compared to adults without T2D [10]. In contrast, a hospital-based study in Atlanta found LTBI prevalence was higher in patients without T2D (14.7%, 5/34) compared to patients with newly diagnosed T2D (9.2%, 9/98) [11], however these results are based on small samples sizes and could be confounded by other underlying health conditions requiring hospital admission. Together, these studies provide evidence for an increased risk of primary infection with Mtb in patients with T2D compared to otherwise healthy individuals.

2.2 T2D increases the risk of active TB

If the host immune response is unable to contain Mtb infection, progression from asymptomatic LTBI to active TB disease can occur. The association between T2D and active TB is well established and has been reviewed elsewhere [12-14]. Accumulating data from 44 studies including prospective, retrospective and case control studies, Al Rifai and colleagues showed that T2D patients had 2-4 fold increased risk of active TB [15]. Cohort studies from low and moderate TB incidence countries, demonstrated more than 2-fold increased TB risk among T2D patients with pooled relative risk (RR) (2.03, 95%CI 1.62–2.55) [9]. The latest WHO report estimates that approximately 350 000 TB cases were attributable to T2D in 2019 [2]. There is now agreement that T2D predisposes individuals to developing active TB and that its contribution to global TB prevalence will increase further with the rise of T2D prevalence. Consequently, several clinical trials for TB preventative therapy in LTBI positive T2D patients have been initiated or are currently ongoing [16,17].

2.3 T2D increases the risk of multi-drug resistant TB

Resistance to antibiotic TB therapy is rising globally with close to half a million TB cases resistant to one of the most potent TB drugs, rifampicin [2]. Of those 78% had multidrug-resistant TB (MDR-TB). Treatment of MDR-TB requires up to 20 months with a global treatment success rate of only 57% [2]. Extensively drug-resistant TB (XDR TB) (resistance to rifampicin, isoniazid, any fluoroquinolone and at least one the following: levofloxacin, moxifloxacin, bedaqualine and linezolid) was identified in close to 13 000 cases in 2019 [2].

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A growing body of literature has linked T2D with an increased risk for MDR-TB. In a meta-analysis including 24 observational studies, Tegene et al. revealed that T2D is associated with higher rates of MDR-TB (OR = 1.97, 95% CI = 1.58–2.45), irrespective of country income level [18]. Similarly, Huangfu and colleagues found that T2D was associated with a two-fold increased risk of MDR-TB among TB patients (OR 1.98, 95%CI 1.51–2.60) based on robust evidence from 104 publications [19].

Using whole genome sequencing to examine drug resistance mutations in Mtb isolates of TB patients with T2D patients, Ruesen et al. demonstrated that T2D was associated with more mutations conferring resistance to isoniazid and ethionamide (Rv1482c-fabG1), fluoroquinolone (gyrA) and rifampicin (rpoB) [20]. The association between T2D and drug resistant mutations was evident even among patients with newly diagnosed TB and is independent of the levels of glycemic control determined by HbA1c [20]. Thus, suggesting that previous anti-TB treatment does not account for the higher risk of MDR-TB in TB-T2D patients.

Interestingly, lower concentrations of isoniazid and pyrazinamide were detected in serum from TB patients with T2D compared to TB patients without T2D [21,22]. These reduced systemic concentrations of antibiotics may contribute to the development of drug resistance. The reasons for lower antibiotic concentrations in T2D patients remain to be elucidated but are likely linked to either body weight distribution due to generally higher BMI in T2D patients or more rapid metabolic breakdown of the TB treatment.

3. T2D increases TB disease severity and the risk of adverse TB treatment outcomes

T2D patients who develop active TB have frequently more severe disease on chest x-ray, delayed culture conversion and higher sputum smear grades [23]. Higher smear grades in patients with TB-T2D co-morbidity are indicative of higher lung mycobacterial burden suggesting that TB patients with T2D are more infectious than TB patients without co-morbidities [23]. A recent study from Brazil confirmed that TB patients with any form of dysglycemia (T2D or pre-diabetes) are more likely to transmit Mtb in a household contact setting [24].

TB patients with T2D frequently have more severe disease on chest X-ray at diagnosis with more cavities and parenchymal lesions [25,26]. Bilateral pulmonary involvement and extensive pulmonary disease was also found on CT scans in TB patients with underlying T2D [27,28]. Huang and colleagues showed that T2D patients with poor glycemic control (HbA1c > 8%) were more likely to present with atypical findings on chest X-ray and thoracic CT scans such as advanced extensive lesions (P< 0.001), more cavities (P< 0.001) and all lobe involvement (P= 0.041) [28]. In contrast, one study found that T2D patients with TB presented with lower lung cavitary lesions compared to TB patients without T2D [29]. Differences in these findings could potentially result from differences in median age and levels of glycemic control in the respective study cohorts. In addition, dyslipidemias may contribute to differential clinical manifestation of TB and have been shown to be highly variable in T2D patients across different ethnicities [7].

Several retrospective studies have demonstrated adverse TB treatment outcomes and higher mortality in TB patients with T2D [19,30]. A recent prospective study following more than 700 individuals from West India showed that T2D significantly increased the risk of early mortality during TB treatment (aHR, 4.36; 95% CI, 1.62–11.76) [31]. A different study also conducted in India surprisingly found that poorly controlled T2D was not associated with higher odds of adverse TB treatment outcomes among TB patients with normal or high BMI and was associated with better TB outcomes among patients with low BMI [32]. These findings highlight that T2D is a complex disease and suggests that subtle metabolic sub-phenotypes (beyond the crude classification of T2D) may be more susceptible or resistant to adverse TB treatment outcomes.

While T2D in Western populations is often associated with obesity, a significant proportion of T2D cases, particularly in Asian populations, do not have a high BMI [33]. A

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prospective cohort study of 225 new pulmonary TB patients with comorbid T2D in India found that low and normal BMI were more common among TB patients with T2D than high BMI (88% vs. 12%) [31]. Similar proportion between T2D with and without low BMI was also reported by Kubiak et al in a cross-sectional analyses of active TB cases in southern India (90.3% vs. 9.7%) [34]. These observation of lower BMI in T2D patients with TB compared to T2D patients are likely confounded by TB-associated wasting. Prevalence of active TB was 12-times higher in obese diabetic adults compared to overweight-obese without T2D and 2.5-times higher in T2D vs. non-diabetic with normal weight and not different among underweight adults [34]. Consistent with this observation several other studies reported that obesity in the absence of hyperglycemia protects against TB [35-37] and individuals with high BMI are less likely to die during TB treatment. Similar observations were made in a murine model [38].

Whether diabetes increases the risk of active TB more profoundly in the overweight and obese population and less so in underweight and low BMI subjects requires further evaluation but carries important implications in Asian populations where T2D develops at lower BMI compared to other ethnicities [33]. Nevertheless, the association between T2D and adverse TB treatment outcomes underscores the need for T2D screening among TB patients at diagnosis and appropriate clinical management of newly diagnosed T2D.

4. Contribution of hyperglycemia to TB disease severity and adverse TB treatment outcomes

4.1 T2D-related chronic hyperglycemia

T2D is characterized by insulin resistance and the progressive loss of beta cell mass and/or function which leads to chronic hyperglycemia [39]. The impact of the severity of hyperglycemia on clinical manifestation of TB and TB treatment outcomes was focus of several studies. Using large primary care data from the UK, Critchley et al. showed that T2D patients with poor glycemic control (HbA1c > 11%) had elevated risk for hospitalization for various type of infections including TB (incidence rate ratio 4.70) irrespective of age [40]. Optimal control of blood glucose (HbA1c 6-7%) reduced risk of hospitalization (IRR 1.41 vs. 4.70), but these well-controlled T2D patients were still at a higher risk compared to matched controls without T2D suggesting that metabolic factors other than hyperglycemia contribute to increased susceptibility to infections in T2D [40]. Poor glucose control also increased the risk of mortality as reported by Chiang et al. in a cohort study in Taiwan. The authors reported higher mortality among TB patients with Hba1c > 9% compared to those with HbA1c< 7% (6 vs. 18%) [41].

Furthermore, poor glucose control worsens the response to TB treatment. Only 47% of TB-T2D patients with an average HbA1c of 10.7% obtained sputum culture conversion by month 2 of TB treatment, compared to sputum culture conversion rates of 73% in TB patients without T2D [29]. Salindri et al. found that well-controlled T2D patients (HbA1c < 8.0%) had faster culture conversion times than those with poorly controlled T2D (HbA1c ≥ 8.0%) in MDR-TB patients [42]. These studies suggest that the adverse effects of T2D on TB disease are attributed at least in part to poor glycemic control and that improving glycemic control may lead to better TB treatment outcomes and reduced risk of relapse and recurrence. However, achieving optimal clinical management of T2D patients in low- and middle-income countries is challenging with currently less than 10% of T2D patients receiving guideline-based comprehensive diabetes treatment [43].

Short versus long term exposure to hyperglycemia could differently impact the host immune responses and TB outcomes. In vitro, incubation of mouse bone marrow derived macrophages (BMDMs) under high glucose condition (25mM Glucose) for short time (48h) has been shown to reduce TNF-α production while a longer incubation time (7 days) released higher TNF-α compared to BMDMs maintain in baseline 5.5mM Glucose [44]. In

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a murine model, Martens et al. showed that chronic (≥ 12 weeks), but not acute (< 4 weeks) hyperglycemia, results in a higher bacterial burden and higher inflammation in the lungs compared to normoglycemic controls [45]. Similarly, Cheekatla et al. showed higher lung bacillary load and pathology in hyperglycemic mice compared to control mice at 6 months, but not at the early 1- and 3-months post infection [46]. These studies used a streptozotocin-induced model of diabetes. A 12-week high-fat diet based murine model of pre-diabetes showed a trend towards higher Mtb burden in animals with impaired glucose tolerance, significantly higher lung pathology scores and impaired cytokine responses both in the lung and in blood [38]. Interestingly, restoration of glucose tolerance while maintaining high body fat conferred resistance to TB in the murine model described above. Immune dysfunction to TB has been confirmed not only in T2D patients, but also in pre-diabetes patients [47].

How hyperglycemia contributes to impaired immune responses to Mtb has been focus of several studies many of them showing functional defects in macrophages including reduced phagocytosis of Mtb and Mtb killing in diabetic macrophages from both human and animal origins [48-51]. Interestingly, monocyte-derived macrophages (MDMs) from obese individuals had higher antigen presenting capacity to stimulate T cells, whereas macrophages from T2D patients displayed compromised intracellular Mtb killing capacity [52]. In a subsequent study, the authors revealed that primary human monocytes from T2D patients had reduced expression of HLA-DR, a marker for antigen presentation. Interestingly, cholesterol levels including total cholesterol, HDL- or LDL-cholesterol were associated with higher HLA-DR expression [53]. These findings highlight that hyperglycemia cannot be studied in isolation without assessing the impact of dyslipidemia in susceptibility of T2D patients to TB.

4.2. Transient TB-induced hyperglycemia

Active TB itself can induce transient stress-hyperglycemia, which usually normalizes with TB treatment and does not require long-term diabetes management. Between 17% and 87% of TB patients who have not been previously diagnosed with T2D, have elevated blood glucose measurements at TB diagnosis [54]. However, it is important to follow TB patients longitudinally throughout TB treatment and determine whether they have indeed newly diagnosed T2D, which requires clinical management, or transient stress hyperglycemia, which resolves with TB treatment. Therefore, only repeated measurements of random or fasting blood glucose and HbA1c throughout TB treatment are confirmative of T2D. The TANDEM study performed such longitudinal follow up of TB patients across four different continents and found that T2D prevalence amongst TB patients was lowest in South Africa (10.9%) and highest in Indonesia (19.7%) [55]. In a different study from South Africa hyperglycemia was transient in the majority of participants with newly diagnosed hyperglycemia, with median HbA1c significantly decreased at 3 months follow-up (5.7% vs. 5.4%, P<0.0001), while patients with pre-existing T2D maintained a high levels of blood glucose 3 months after treatment (4.6% vs. 4.7%) [56].

A recent systematic review including eleven studies with a total of 677 (27,3%) of patients with newly detected hyperglycemia at baseline, revealed that the total pooled burden of hyperglycemia at 3-6 months follow up was 11% [57]. These data suggest that a high proportion of TB patients with elevated blood glucose levels at baseline have transient hyperglycemia that can be resolved following effective TB therapy. Stress hyperglycemia even in absence of T2D is a predictor of mortality during sepsis [58]. Therefore, further studies are urgently needed to comprehensively assess TB treatment outcomes and relapse risk in TB patients with transient hyperglycemia.

5. Hyperinsulinemia and TB disease severity

Hyperinsulinemia is described as elevated concentrations of circulating insulin in the blood due to insulin resistance and is common in obesity and the early stages of T2D.

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Hyperinsulinemia goes hand in hand with hyperglycemia and dyslipidemia in T2D, therefore its independent contribution to TB susceptibility is difficult to assess. In addition, most studies on TB and T2D do not measure fasting insulin levels in patients, therefore there are few reports in the literature on the association between serum insulin concentrations or insulin resistance and TB disease severity. A recent study among TB patients with T2D stratified patients according to degree of insulin resistance and showed that the degree of insulin resistance reflects TB disease severity [59]. Whether elevated insulin concentrations and insulin resistance impacts TB manifestation in patients without T2D remains to be elucidated. However, high fat diet fed mice with hyperinsulinemia and impaired glucose tolerance had more severe lung pathology compared to control animals even in absence of full-blown diabetes [60]. Insulin can have both pro- and anti-inflammatory properties and is a known modulator of immune function [61]. Reports of T2D patients developing a TB granuloma at the site of insulin injection suggests that insulin may contribute TB reactivation [62]. Whether hyperinsulinemia is linked to more severe TB disease and adverse TB treatment outcomes remains to be elucidated.

6. Dyslipidemia and TB disease severity: Cholesterol vs. triglycerides

T2D is not only characterized by hyperglycemia and hyperinsulinemia, but also by hyperlipidemia. To complicate matters, the form of dyslipidemia is highly variable in T2D patients across different ethnicities. For instance, TB household contacts with T2D patients in South Africa have mainly elevated cholesterol, while diabetic TB contacts in South Texas have mainly elevated triglycerides [7]. The relative contribution of these different forms of dyslipidemia to susceptibility to TB remain to be investigated.

However, there is some evidence suggesting that elevated cholesterol is protective in the context of TB. A large population-based longitudinal study from South Korea including more than 5 million participants from 2009 to 2018, identified a clear relationship between low total cholesterol levels and high TB risk. Interestingly, the correlation was seen less robust in T2D and obesity and was lost in subjects receiving statins [63] suggesting that altered lipid profiles in metabolic conditions (obesity, T2D) or with drug treatment (Statin) can affect the susceptibility to TB. In active TB patients, cholesterol concentrations are generally lower compared to healthy controls possibly aggravated by TB-associated wasting, nevertheless cholesterol is a reliable indicator of TB disease severity. For instance, radiological extent of disease inversely correlated with both HDL and LDL but was not associated with sputum smear grading [64]. Low LDL and HDL were associated with granuloma necrosis and fibroplasia leading to exacerbated lung damage in TB patients and especially those with T2D [65]. Higher serum cholesterol concentrations on the other hand were linked to lower concentrations of serum inflammatory markers and TB-related mortality, and this was independent of BMI [66].

In contrast to the seemingly beneficial effect of cholesterol on TB disease severity, elevated triglycerides appear to be associated with adverse TB treatment outcomes. Higher triglyceride concentrations and lower concentrations of cholesteryl esters were found in TB patients who subsequently failed treatment compared to those who were cured, with two cholesterol esters (16:0 and 18:2) having predictive accuracy of treatment failure at TB diagnosis [67].

The underlying mechanisms addressing the association between high cholesterol levels and reduced TB disease severity are not well elucidated. Cholesterol is essential for phagocytosis of Mtb by macrophages [68] and elevated total cholesterol can result in elevation of specific oxidized cholesterols that have shown to both increase phagocytosis, but also reduce growth of Mtb and *Mycobacterium bovis* BCG in human monocytes [69]. Moreover, in-vitro supplementation with cholesterol leads to an upregulation of HLA-DR expression in human blood monocytes [70] possibly facilitating antigen presentation.

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Consistent with this, ex vivo phenotyping of human monocytes revealed that while triglycerides are associated with reduced HLA-DR cholesterols counterbalance this effect [53].

Conflicting data have been published about the connection between a cholesterol rich diet and TB. One study showed that adult TB patients receiving a cholesterol-rich diet experienced accelerated sterilization of sputum Mtb cultures during TB treatment relative to controls receiving a normal diet [71]. Other population-based study in Singapore reported that a high cholesterol diet could increase TB risk [72] in line with a preclinical study showing that hypercholesterolemia impairs immunity to TB in a murine model [73].

7. Impact of T2D treatment on TB outcomes

T2D patients are frequently on both glucose lowering and lipid lowering medication. Two of the most frequently used T2D treatments metformin and statins have been evaluated in relation to TB disease severity and treatment outcomes and have recently received attention as possible candidates for host-directed therapy for TB treatment.

7.1. Metformin

Metformin is a glucose lowering agent widely used among patients with T2D. Metformin use in T2D patients was associated with lower LTBI prevalence. Magee et al found that using metformin plus two or more other diabetes medications was associated with lower odd of LTBI (adjusted OR 3.9, 95% CI 1.1–13.8) compared to those without any diabetes medication [74].

Metformin use was also associated with lower risk of developing active TB among TB contacts with T2D [75,76]. T2D patients who included metformin in their treatment strategy had significantly lower risk of TB compared to those not using metformin. In contrast, insulin users had a significantly higher risk of TB compared to those without insulin use [76]. A recent large study involving over 75,000 T2D patients confirmed the protective effect of metformin, however only at the highest cumulative dose, whereas lower metformin doses did not reduce the incidence of active TB within a timeframe of two years [77]. In TB patients, metformin use was associated with significantly improved sputum culture conversion rates, fewer pulmonary cavities and reduced mortality rates [31,78,79]. Importantly, these positive effects have been shown to be independent of the degree of blood glucose control [79] suggesting other possible underlying mechanisms mediated by metformin besides direct effects on blood glucose control could underpin the improvement of TB outcomes.

Mechanistically, it has been previously shown that metformin activates adenosine monophosphate–activated protein kinase (AMPK) [80], a regulator of cellular autophagy [81] which is crucial for an effective host innate immune response against intracellular pathogens such as Mtb. Singhal and colleagues showed that metformin inhibits intracellular Mtb growth by inducing ROS and autophagy [78]. Furthermore, Lachmandas et al. observed strong upregulation of genes involved in phagocytosis and ROS production in PBMC treated *ex vivo* with metformin [82]. In a murine model metformin reduced Mtb burden in the lung (both as monotherapy and in conjunction with anti-mycobacterials) and improved lung pathology [78].

A beneficial effect of metformin on *in vivo* Mtb clearance was also shown by Bohme et al. In Mtb-infected mice that received metformin along with pyrazinamide and isoniazid for 30 days, bacterial burden was compared to mice having received only pyrazinamide and isoniazid [83] confirming that metformin can enhance the sterilizing activity of available antimicrobial treatment for Mtb infection. Conducting subsequent mechanistic experiments, the authors revealed that metformin enhances the host immune function against Mtb via reprograming CD8(+) T cell metabolism, favoring in the expansion of memory CD8+CXCR3+ T cells population with anti-Mtb properties. The increased frequency of this distinct memory T cell phenotype has been consistently observed in both metformin-treated mice as well as in PBMC from metformin treated T2D patients [83].

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A question remains whether the beneficial effects of metformin can only be achieved in TB patients with T2D or whether metformin can also improve TB outcomes in non-diabetic subjects. There is no data yet from ongoing human clinical trials. Preclinical studies however show conflicted results. While Singhal et al. reported a reduction of lung bacillary load in euglycemic mice receiving metformin either alone or in combination with TB drugs [78], a recent study reported that metformin improves TB severity only in hyperglycemic mice and not in non-diabetic control animals [84]. The authors showed that treatment of diabetic mice with metformin reduced lung Mtb burden by ~1.5log CFUs compared with untreated hyperglycemic mice, but strikingly augmented lung bacterial loads and immunopathology in nondiabetic mice [84]. Another study provided evidence that metformin has no significant effect on mice receiving the first-line TB regimen [85]. Taken together, these results, further consolidate the evidence that hyperglycemia itself increases TB severity and suggest that metformin may be beneficial for improving TB severity and treatment outcomes at least in patients with TB and T2D comorbidity. Data from clinical trials assessing the utility of metformin as adjunct TB treatment in non-diabetic patients are urgently needed to conclusively confirm or disregard metformin as host-directed TB therapy.

7.2. Statins

Statins lower cholesterol levels by inhibiting the 3-hydroxy-3-methylglutaryl-CoA reductase, one of the key enzymes in the generation of cholesterol, but also have anti-inflammatory properties. Statins are one of the most frequently prescribed drugs to reduce morbidity and mortality in patients with hypercholesterolemia, coronary heart disease, T2D patients and in patients suffering from infectious diseases [86-88].

Statin therapy significantly reduced the risk of TB in T2D patients by 22% (pooled RR 0.78, 95% CI 0.63–0.95) and TB patients without T2D by 40% (pooled RR 0.60, 95% CI 0.50–0.71) [89]. Pan et al, demonstrated that statin use was associated with a 35% decreased risk of TB (crude HR, 0.648; 95% CI, 0.430–0.976) compared with no statin use as the reference group [90]. Macrophages isolated from patients with hypercholesterolemia receiving daily statin therapy and infected with Mtb in vitro, had significantly lower Mtb growth 3 days post infection compared to the controls [91]. Statin therapy in mice lead to a reduction in Mtb burden in the lung, liver and spleen at 4 weeks and 8 weeks post infection compared with mice that received vehicle control [91]. This was further confirmed by Skerry et al, who demonstrated the treatment of Mtb-infected macrophages with simvastatin significantly reduced bacterial load compared to vehicle, and this was further enhanced the bactericidal activity of isoniazid [92]. In chronically infected mice (6 weeks post infection) receiving a standard oral treatment regimen of rifampicin, isoniazid and pyrazinamide, along with simvastatin, demonstrated greater bacillary killing in the lungs, compared to treatment without simvastatin at 4 weeks ($p<0.01$) and 8 weeks ($p<0.01$) of treatment [92]. However, in a retrospective study in South Korea, there was no evidence that the use of statins provided a protective effect on TB incidence (aHR 0.98; 95%CI 0.89–1.07). Differences in these results may be due to ethnicity of participants, baseline metabolic characteristics of the participants and trial interventions [93].

Combined metformin and statin use in patients with diabetes was associated with less than half the prevalence of LTBI (4% combined metformin/statin) compared to no treatment (10%) [74]. There may be benefits for patients with T2D at risk of LTBI using a combination therapy of both metformin and statins as preventing LTBI is an essential step for preventing active TB disease and both LTBI and TB are complicated by T2Ds [74].

A schematic summary of the relative contribution of hyperglycemia, elevated cholesterol and triglycerides is shown in the graphical abstract.

6. Conclusions

The increased risk of T2D patients to primary infection with Mtb, to progression from LTBI to active TB and adverse TB treatment outcomes is undisputed. While previously hyperglycemia was thought to be the main driver of increased susceptibility to TB, there is now mounting evidence that other host metabolic factors such as hypercholesterinemia and elevated triglycerides further contribute to susceptibility to TB in T2D patients. In contrast, high cholesterol is suggested to have a favorable effect on clinical manifestation and outcomes of TB. Further studies are needed to fully dissect the relative contribution of the metabolic drivers on immune responses to Mtb.

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