



The potential role for metformin in the prevention and treatment of tuberculosis

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Tuberculosis remains an ongoing health threat worldwide (1). The ability of this intracellular bacterial pathogen to evade the host's innate and adaptive immune responses allows it to establish persistent intracellular infections (2). Spread through respiratory droplets, the disease primarily causes lung infection; however, pulmonary tuberculosis can disseminate throughout the body, leading to devastating health consequences (3). According to the World Health Organization, nearly 2 billion people worldwide are infected with *Mycobacterium tuberculosis* (*M. tuberculosis*); this is equivalent to about a quarter of the world's population (1). While not all individuals infected with *M. tuberculosis* develop disease, those with HIV, diabetes, and other risk factors, such as smoking, alcohol consumption, and malnutrition, have a higher probability of presenting with active infection (1). In 2020, an estimated 9.9 million people throughout the world developed tuberculosis, and approximately 1.3 million died with this disease (1). The countries with the highest burden of incident cases included Southeast Asia (43%), Africa (25%), the Western Pacific (18%), Eastern Mediterranean (8.3%), the Americas (3.0%), and Europe (2.3%) (1).

Drug resistance is a well-known problem in the treatment of *M. tuberculosis* infections. Drug-resistant tuberculous bacilli are resistant to either isoniazid or rifampicin, two first-line anti-tuberculous medications, and multidrug-resistant bacilli are resistant to both medications (1). Throughout the world, the frequency of drug-resistant and multidrug-resistant tuberculosis has remained relatively stable for over 10 years (1). In patients

with an initial diagnosis of tuberculosis, 3–4% have drug resistance (1). In patients previously treated for tuberculosis, the percentage of drug-resistant cases can reach 18–21% (1). This situation indicates the need for new drug development, different treatment regimens with current medications, and/or the use of adjunctive therapy with current medications.

Diabetes mellitus (DM) triples the risk of developing tuberculous infection and leads to increased disease severity and mortality (4). The poor clinical outcomes observed in patients with diabetes and tuberculosis can be explained in part by the suppressive effects of hyperglycemia on innate and adaptive immune responses (5). As reported by the World Health Organization in 2014, diabetes affects an estimated 422 million people globally; this number continues to increase as does the number of overweight and obese individuals who are at risk to develop diabetes (6). Patients with type 2 DM have several metabolic abnormalities, including hyperglycemia, elevated pro-inflammatory cytokine levels, and increased oxidative stress (7). These effects could adversely affect host defense responses to tuberculosis, and their reversal might explain the possible benefits of some diabetic medications. For example, metformin has several host-directed therapeutic effects, including increased host-mediated autophagy responses, reduced excess inflammation, and enhanced immune cell function (7,8). Modulation of host cell responses in addition to direct targeting of the pathogen by conventional anti-tuberculous medication could lead to better treatment outcomes in patients with tuberculosis and decrease the development of drug resistance (9).

Metformin can prevent the establishment of tuberculous infections

Several studies have suggested that metformin can reduce the establishment of tuberculous infections in diabetic patients. A retrospective case-control study by Marupuru *et al.* (10) analyzed 451 hospitalized patients comparing diabetics on metformin, diabetics not on metformin, and healthy subjects. Infection with tuberculous bacilli occurred more frequently in diabetics with higher HbA1c levels (>8%). Metformin dosages of 500 and 1,000 mg daily both significantly reduced the risk of tuberculous infection and had significant protective effects against tuberculosis (10).

A cross-sectional study using the National Health and Nutrition Examination Survey data from the United States found that combined metformin and statin use in diabetic patients was associated with less than half the prevalence of latent tuberculous infection (LTBI) identified by positive tuberculin skin tests, suggesting that combination therapy of metformin and other medications without antimicrobial effects might reduce the risk of latent infection in some individuals (11). In this study, metformin alone did not appear to have a protective effect, but metformin with 2 or more other diabetic medications did. Singhal *et al.* (12) prospectively studied 220 patients with diabetes, including 62 patients with latent tuberculosis infection. In this cohort, metformin treatment was associated with reduced T-SPOT[®]. TB test (Oxford Immunotec, Oxfordshire, UK) reactivity when compared to patients treated with other diabetic medications (25.6% *vs.* 42.4%). In addition, diabetics treated with metformin had a larger number of interferon- γ secreting T cells specific for the mycobacterial culture filtrate protein-10 (CFP-10) antigen. Since the prevention of LTBI is essential to prevent tuberculosis, metformin could be considered a medication that lowers the incidence of both LTBI and tuberculous disease in diabetic patients and might be especially useful in patients with diabetes who live in regions with high case rates of tuberculosis.

Metformin may prevent the development of tuberculous disease in patients who have latent tuberculosis

In addition to reducing the frequency of LTBI, some studies have suggested that metformin can reduce the development of active disease. A retrospective cohort study by Lee

et al. (13) found that diabetic patients with close contact to active cases not using metformin had significantly more incident tuberculosis than those using metformin and those without diabetes. Among 5,846 close contacts, 755 per 100,000 metformin users, 1,117 per 100,000 metformin non-users, and 526 per 100,000 healthy contacts developed active tuberculosis within 2 years following contact, indicating a protective effect of metformin against disease (13). A retrospective cohort study by Lin *et al.* (14) also reported a significantly lower incidence of active disease in type 2 DM patients using metformin than in type 2 DM patients not using metformin. In metformin users, a higher cumulative defined daily dose appeared to have a larger protective effect (14). Lee *et al.* (15) reported that patients with high-dose metformin use (>150 cumulative defined daily doses) had a significantly lower risk of incident tuberculosis than patients with low-dose metformin use (90–150 cumulative defined daily doses), but both dose ranges had protective effects against active disease. Therefore, these two studies suggest that metformin has a dose-dependent effect in the prevention of tuberculous disease in diabetic patients (14,15).

Another retrospective cohort study compared the effect of metformin and sulfonylureas, both considered first-line treatment options for type 2 DM, in reducing the risk of tuberculosis in 40,179 patients with type 2 DM (16). Two years of metformin therapy, but not sulfonylurea therapy, significantly reduced the development of tuberculosis in diabetic patients (16). Another retrospective cohort study supported these results and reported that metformin use in elderly patients (≥ 60 years) with DM lowered the risk for tuberculosis compared to sulfonylurea use (17). Since metformin and sulfonylureas both have similar effects on glycemic control, these studies suggest that metformin reduces the risk of tuberculosis by some mechanism other than its blood glucose lowering effect (16). Collectively, these results indicate that metformin may protect some DM patients from developing active disease and therefore might be considered a preventive measure against tuberculosis in diabetic patients. For example, it is possible that the combination of metformin and isoniazid would reduce the risk of active disease more than isoniazid alone in patients with LTBI. Testing this possibility would require a relatively simple study design but would require a large number of patients with a multiple year follow-up.

Metformin can change the disease course in active tuberculosis

Metformin also appears to modulate the course of pulmonary disease in patients with active tuberculosis, leading to enhanced immune responses and improved treatment outcomes. A retrospective cohort study by Ma *et al.* (18) evaluated the clinical outcomes of 58 diabetic patients either on metformin or not on metformin during standard anti-tuberculous treatment. A higher treatment success rate [93.8% *vs.* 71.4%, probability (P)—not significant], a higher proportion of culture conversions by the end of 2 months (87.5% *vs.* 71.4%, P—not significant), and lower relapse rates within 3 years (6.3% *vs.* 35.7%, $P=0.045$) occurred in patients on metformin in combination with an anti-tuberculous medication. The beneficial effect of metformin on the disease course is also supported by an observational study that examined two groups of type 2 DM patients with tuberculosis; one group received 1,000–1,500 mg metformin with insulin and anti-tuberculous medications and the other received only insulin and anti-tuberculous medications (19). One hundred percent of patients in the metformin group had negative acid-fast bacillus smears after 2 months of treatment, but only 75% of the non-metformin group had negative smears ($P=0.046$) (19). In addition, patients on metformin had increased autophagy based on higher serum levels of Microtubule Associated Protein 1 Light Chain 3 Beta, increased super oxide dismutase levels, and increased interferon- γ levels. Lee *et al.* (20) reported patients with DM and cavitary pulmonary tuberculosis taking metformin in combination with anti-tuberculous medications had significantly higher sputum culture conversion rates after 2 months of treatment compared to patients on no metformin. In these studies, metformin increased the bactericidal effects of anti-tuberculous medication and improved outcomes in diabetic patients.

Abinaya and coauthors randomized 100 nondiabetic patients with pulmonary tuberculosis into two groups (21). The control group received conventional anti-tuberculous treatment; the experimental group received the same treatment and metformin at 250 mg twice daily. The average time to sputum smear conversion was 3.4 weeks in the metformin group and 4.7 weeks in the control group ($P=0.012$). At the end of 2 months, the drug resistance studies indicated that 1 patient in the metformin group had resistance to rifampicin and 4 patients in the control group

had resistance to anti-tuberculous medications (3 patients to rifampicin and 1 patient to isoniazid). Four patients in the control group and 6 patients in the metformin group had adverse events, mostly gastrointestinal related symptoms, such as nausea and vomiting. No significant differences in routine laboratory tests, including complete blood counts, renal function tests, and liver enzymes, occurred between the two groups. This study indicates that the use of metformin in patients on conventional therapy accelerates sputum conversion and possibly limits the development of drug resistance (21). In addition to improving clinical treatment outcomes, a prospective study of diabetic patients with tuberculosis reported that 500 mg of metformin twice daily improved the patients' perceptions of quality of life in several domains, including symptom resolution, mental status and interest in work/activities, and exercise (22).

The attached table summarizes the clinical studies reviewed in this editorial (Table 1).

The effect of metformin on the pathogenetic factors in tuberculosis infections

Matrix metalloproteases (MMPs), a family of enzymes with proteolytic and cell recruiting activity, contribute to lung tissue destruction and disease severity in tuberculosis (23). MMPs may contribute to pulmonary cavitation in tuberculosis, which is usually associated with a higher bacillary burden, delayed sputum culture conversion, and the development of drug resistance (23). Metformin therapy lowers systemic MMP-1, -2, -3, -7, -9 and -12 levels in diabetic patients with tuberculosis and could possibly decrease MMP-mediated tissue destruction in tuberculous patients without DM (24). Furthermore, patients with diabetes and tuberculosis have higher levels of systemic monocyte activation markers, including soluble cluster of differentiation 14 (sCD14), soluble CD163 (sCD163), soluble tissue factor (sTF), and C-reactive protein (CRP), indicating increased inflammatory responses of monocytes and macrophages contributing to tissue damage and progression of pulmonary disease (25). Specifically, Kumar *et al.* (25) showed that sCD14 and sCD163 levels were higher in diabetic patients with bilateral versus unilateral disease and cavitary versus non-cavitary disease and thus are associated with increased disease severity and bacterial burden. In diabetic patients on metformin therapy, the levels of sCD14, sCD163, and CRP were significantly

Table 1 Retrospective and prospective studies on metformin and tuberculosis

Author, year, country/region	Study design	Time frame	Met vs. no Met	Outcome
Retrospective studies				
Lee, 2018, Taiwan (15)	Retrospective: analysis of region wide data base, new diagnosis of DM; propensity matched	Incident TB, 2003–2006	88,866 DM cases with Met use, 88,866 DM cases with no Met use	127 cases per 100,000 on Met, 140 cases per 100,000 no Met, HR =0.84
Lee, 2019, Taiwan (13)	Retrospective: analysis of region wide database, close contacts of active case with DM and normal renal function; propensity matched	Incident TB, within 2 years of contact	Met >90 daily doses during year prior to contact date, 5,846 users	526 cases per 100,000 in healthy controls, 755 cases per 100,000 in DM on Met, 1,117 cases per 100,000 in DM not on Met
Lin, 2018, Taiwan (14)	Retrospective: analysis of region wide database with new diagnosis of DM; propensity matched	Incident TB, 1998–2010	5,026 Met users, 5,026 non-users	Adjusted HR =2.01 (1.80–2.25) for TB in DM cases, adjusted RR =0.24 for TB with Met use
Marupuru, 2017, India (10)	Retrospective: case control DM with TB; DM without TB	2015–2016 hospitalized patients	152 cases, 299 controls	On Met, OR for TB =0.256; HbA1c <7, OR for TB =0.52
Ma, 2018, China (18)	Retrospective: TB treatment centers	Treatment outcome, 3-year follow-up	58 patients with DM, 16 on Met, 42 on no Met	Treatment success: 93.8% vs. 71.4%; culture conversion: 87.5% vs. 71.4%; relapse: 6.3% vs. 35.7% (P=0.045)
Lee, 2018, South Korea (20)	Retrospective: TB + DM; multivariate analysis	Treatment outcome, 1-year follow-up	62 Met, 43 no Met	Sputum conversion higher in cavitory TB on Met, OR =10.8
Pan, 2018, Taiwan (16)	Retrospective: multivariate analysis	TB incidence, 6.1 years follow-up	3,161 on Met, 3,161 on sulfonylureas	TB incidence, adjusted HR =0.337, dose dependent reduced risk with Met
Park, 2019, South Korea (17)	Retrospective: patients >60 years old; propensity matching	TB incidence, 11 years follow up	12,582 on Met, 12,582 on sulfonylurea	TB incidence 280.2 per 100,000 on Met, 394.5 per 100,000 on sulfonylurea, HR =0.74
Singhal, 2014, Singapore (12)	Retrospective: TB with DM; multivariate analysis	Treatment outcome	109 Met, 164 no Met	Met patients fewer cavities on X-ray (P=0.041), mortality—Met 3%, no Met 10% (P=0.013)
Prospective studies				
Novita, 2019, Indonesia (19)	Prospective study: RCT; TB + DM	Treatment outcome, 6 months TB treatment	22 Insulin+ Met, 20 Insulin + no Met	Sputum reversion at 2 months, 22 Met vs. 15 no Met (P=0.046)
Abinaya, 2020, India (21)	Prospective: RCT; no DM	Treatment outcome, 6 months TB treatment	50 Met, 50 no Met	Sputum conversion: 3.4 weeks on Met vs. 4.7 weeks on no Met (P=0.012)
Singhal, 2014, Singapore (12)	Prospective: DM; multivariate analysis	LTBI in cohort	62 DM + LTBI	On Met T-spot reactivity 25.6%, on no Met T-spot reactivity 42.4%, P<0.05

Table 1 (continued)

Table 1 (continued)

Author, year, country/region	Study design	Time frame	Met vs. no Met	Outcome
Mishra, 2021, India (22)	Prospective	2018–2019, treatment outcome, 6 months treatment	48 Met, 48 no Met	HRQoL score improved at end of intensive treatment (P<0.001) and at end of treatment (P=0.001)
Cross sectional studies				
Magee, 2019, USA (11)	Cross sectional study: NHANES	2011–2012, 4,958 DM + QuantiFERON result	LTBI cohort	LTBI lower in DM plus Met + ≥2 DM drugs; LTBI lower in DM on pravastatin

Met, metformin; TB, tuberculosis; DM, diabetes mellitus; HR, hazard ratio; RR, risk ratio; OR, odds ratio; RCT, randomized controlled trial; LTBI, latent tuberculous infection; HRQoL, Health-Related Quality of Life; NHANES, National Health and Nutrition Examination Survey.

decreased compared to those not on metformin. By modulating monocyte activation, metformin has an anti-inflammatory effect that could help decrease disease severity in these patients (25).

Several *in vitro* studies with peripheral blood mononuclear cells (PBMCs) have provided evidence of improved immune responses associated with metformin treatment that could provide the basis for improved clinical outcomes (12,26). Lachmandas *et al.* (26) studied PBMC function in blood samples from 11 healthy patients on 1,000 mg metformin twice daily. Metformin decreased the release of inflammatory markers, such as tumor necrosis factor- α , interleukin (IL)-1 β , IL-6, interferon- γ , and IL-17, from PBMCs and also increased macrophages' phagocytic capacity and reactive oxygen species (ROS) production, indicating enhanced microbicidal ability (26). The increased phagocytic and oxidative abilities of PBMCs due to metformin could reduce the ability of the mycobacterial bacilli to escape from phagolysosomes and resist oxidative bursts; this would help control disease progression in patients both with and without diabetes. In another *in vitro* study Singhal *et al.* (12) examined the human monocytic cell line THP-1 (a spontaneously immortalized monocyte-

like cell line) and human monocyte-derived macrophages and found that metformin treatment inhibited intracellular growth of tuberculous bacilli by inducing mitochondrial ROS production. Both these *in vitro* studies suggest that increased mitochondrial ROS production associated with metformin treatment helps control tuberculous infections (12,26). *Figure 1* provides an overview of the effects of metformin on host defenses relevant to tuberculous infections (12,23-26).

In summary, the studies used in this literature review suggest that metformin can reduce the establishment of LTBI after the exposure to active cases, reduce the progression of LTBI to active disease, modulate the course of active pulmonary disease by increasing sputum conversion rates and reducing tissue injury, and improve health-related quality of life in patients. Therefore, these studies support the use of metformin in patients, especially patients with diabetes, with tuberculous disease. Additional studies should be conducted to better evaluate metformin's immunomodulatory effects in humans, especially when used as adjunctive therapy with first-line anti-tuberculous medication. Randomized control trials are essential to study the use of metformin in patients with both latent

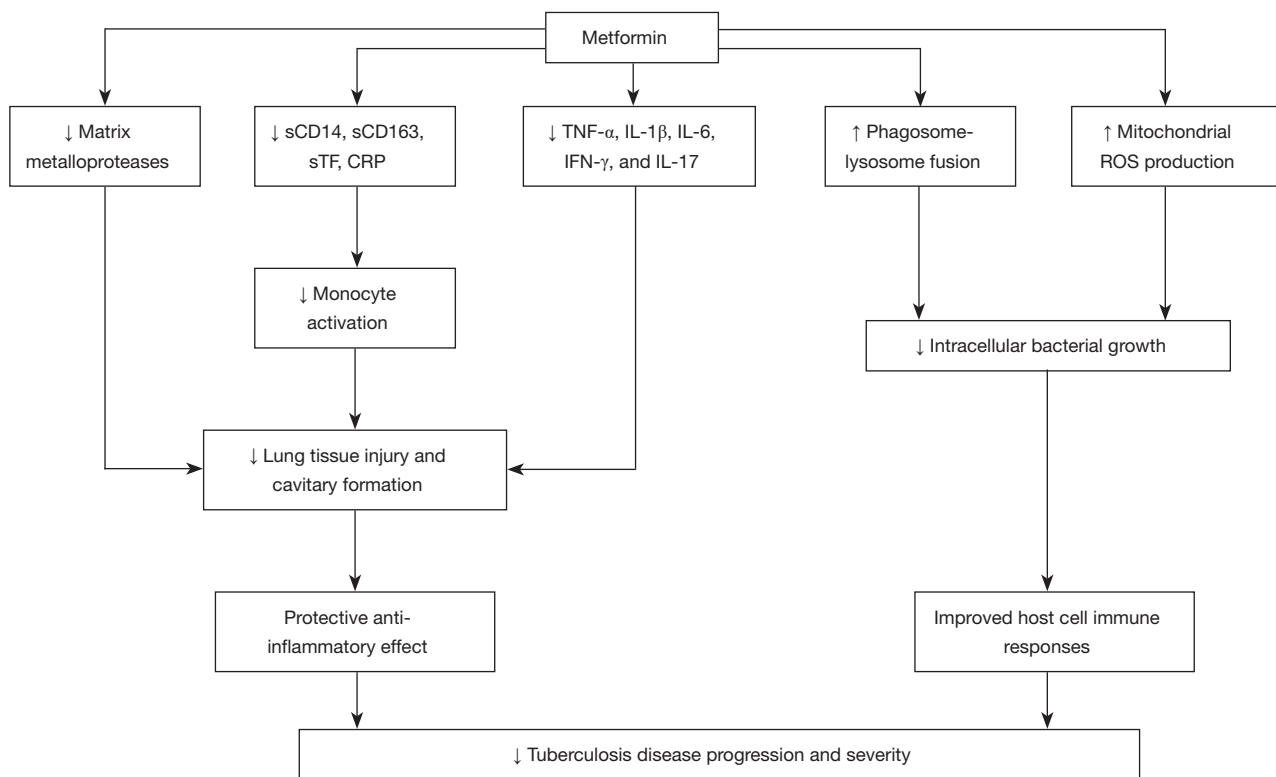


Figure 1 Summary of metformin's host-directed immunomodulatory effects. Metformin decreases production of MPPs and systemic monocyte activation markers, including sCD14, sCD163, sTF, and CRP (24,25). A reduction of inflammatory mediators, including TNF- α , IL-1 β , IL-6, IFN- γ , and IL-17, also contributes to metformin's ability to limit lung tissue destruction, decrease bacillary numbers, and reduce cavity formation (23,26). Furthermore, metformin augments host cell immune responses by enhancing phagocytosis and increasing mitochondrial ROS production (12,26). Through these host-directed therapeutic effects, metformin could improve intracellular killing of tuberculosis bacilli and limit the development of tuberculous infection and disease. sCD14, soluble cluster of differentiation; sCD163, soluble CD163; sTF, soluble tissue factor; CRP, C-reactive protein; TNF- α , tumor necrosis factor-alpha; IL, interleukin; IFN- γ , interferon-gamma; ROS, reactive oxygen species; MPPs, matrix metalloproteases.

tuberculosis and active infection.

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Footnote

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