

Repurposing of Metformin for the prevention and treatment of Tuberculosis

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The bidirectional relationship between tuberculosis (TB) and diabetes mellitus (DM) is a major concern for medical professionals and epidemiologists as DM affects the severity, progress and outcome of TB and vice versa. Patients affected with TB have a higher rate of morbidity, treatment failure and mortality. Likewise, DM triples the risk of contracting TB and therefore poses a threat to the progress made in the reduction of TB incidence. Hence, it is pivotal to address both the diseases keeping in mind the each other. It is known that adjunct therapy with immunomodulatory drugs can enhance TB immunity among diabetic patients. Metformin, a commonly used anti-diabetic drug with adenosine monophosphate-activated protein kinase (AMPK) activation property, has shown the capacity to reduce the growth of *Mycobacterium tuberculosis* within the cell. This drug inhibits the mitochondrial complex and possesses anti-inflammatory action. Therefore, Metformin can be considered as an ideal molecule for host-directed or host-targeted therapy for TB.

Keywords: AMPK activator. Diabetes. Metformin. Tuberculosis.

INTRODUCTION

Tuberculosis (TB) is a fatal infectious disease affected by *Mycobacterium tuberculosis* (*Mtb*). TB is predominantly considered as a disease of the respiratory system. However, it may also affect the central nervous system, vascular, genitourinary system, lymphatic system, bones and the joints (Smith, 2003). TB is an airborne infection present worldwide and is known to have affected humans for 4000 yrs (Zaman, 2010). Genetic studies could identify the evidence of TB even in Egyptian mummies (Ziskind, Halioua, 2007). It is a highly contagious respiratory disease and environmental

factors, as well as the immuno-competency of the host, poses a profound risk of the illness (Barberis *et al.*, 2017).

In the early days, TB was more common among the urban poor (Chang *et al.*, 2011) the rising prevalence of tuberculosis (TB). On the other hand, the improvement in sanitation and nutrition, reduction in crowding, TB vaccination and discovery of streptomycin markedly diminished TB incidences (Dooley, Chaisson, 2009). During the 20th century, the incidence of TB was high in Europe and North America. However, the discovery of short-course treatment including the five antibiotics in 1940 and the increase in the accessibility and availability of free medicine resulted in a large reduction in the incidence of TB (Zaman, 2010). Although these strategies helped in the decline of TB incidences in many developed countries, they failed to do so in developing countries (Chadha, 2009).

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World Health Organization (WHO) reported that 10 million new cases of TB occurred worldwide in 2018. Out of this, 5.7 million cases were in men, 3.2 million were in women and 1.1 million were children. About 66% of the new cases of TB are accounted for from eight countries such as India, China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh, and South Africa. During 2018, 1.5 million died from TB disease; among these, 95% of TB deaths occurred in low and middle-income countries. Globally, 0.48 million people infected with rifampicin-resistant TB (RR-TB) in 2018 and among that 78% had multi-drug-resistant - TB (MDR-TB). Of these cases of MDR-TB, 6.2% were found to be extensively drug-resistant TB (XDR-TB) (Global Tuberculosis Report 2019; Vashisht, Brahmachari, 2015). According to the United States Agency for International Development's (USAID), 2.79 million people became ill from TB and 435,000 died in India (USAID; 2017). The country also has the greatest number of MDR-TB. Besides, there were many undetected and unreported cases of TB as well (Raizada *et al.*, 2015; Uplekar, Pathania, Raviglione, 2001).

At present, standard chemotherapy includes using a combination of antibiotics for six months. Although these drugs are readily available in India, it is yet to reduce the TB incidence primarily due to the lack of awareness and access to treatment (Sachdeva *et al.*, 2012). Moreover, mutated strains of TB bacteria have shown enhanced drug tolerance, thus making the existing antibiotics ineffective (Vashisht, Brahmachari, 2015).

DIABETES MELLITUS – A MAJOR HEALTH PROBLEM

Diabetes mellitus (DM) is another condition with numerous complications and carries the risk of premature mortality (Roglic *et al.*, 2005). According to the ninth edition of the Diabetes Atlas of International Diabetes Federation (IDF), 463 million people had DM globally and this is predicted to rise to 700 million by 2045 (Global Report on Diabetes, 2016). Diabetes caused 4.2 million deaths in 2019 (Global Report on Diabetes, 2016; International Diabetes Federation, 2019). Individuals affected with DM mainly die due to renal or cardiovascular diseases (Morrish *et al.*, 2001). Therefore, there appears to be a serious underestimation of

mortality due to DM as the cause of death is often attributed to the above-mentioned conditions (Fuller *et al.*, 1983). The disease is either caused by impaired or lack of production of insulin by the pancreas or due to the body's inability to utilize the insulin produced. Increased incidences of obesity-associated with raising living standards, lifestyle changes, urban migration, and rapid industrialization are some of the predisposing factors for DM (Kaveeshwar, Cornwall, 2014). Untreated or improperly treated DM often leads to many complications (Global Report on Diabetes, 2016) as diabetes progressively damages the blood vessels, kidneys, nerves, eyes, and heart, resulting in decreased blood flow to different parts of the body. Reduced blood flow and nerve damage often end up in complications such as peripheral neuropathy, nephropathy and retinopathy.

India, at present, bears a burden of more than 62 million cases of DM (Kaveeshwar, Cornwall, 2014). Diabetic prevalence is high among South Asian countries and attributed to the 'Asian Indian phenotype'. This is a peculiar metabolic feature of Asian Indians characterized by a propensity to excess visceral adiposity, dyslipidemia with low high-density lipoprotein (HDL) cholesterol, elevated serum triglycerides, increased low-density lipoprotein (LDL) cholesterol, and an ethnic (possibly genetic) susceptibility to diabetes. According to geography (Kaveeshwar, Cornwall, 2014), there is also a difference in the pattern of DM incidence. Results of a community-based study conducted by the Indian Council of Medical Research (ICMR) showed that the North Indian states (Chandigarh 0.12 million, Jharkhand 0.96 million) have less incidence of DM as compared to the West and South Indian states (Maharashtra 9.2 million, Tamil Nadu 4.8 million) (Anjana *et al.*, 2011; Harries, Billo, Kapur, 2009)

MUTUAL IMPACT OF DIABETES AND TUBERCULOSIS

Numerous epidemiological studies have explained the relationship between DM and TB and the nature of their interaction. These two diseases have many metabolic similarities, as well (Restrepo, 2016). For example, the underlying pathologies of both the diseases are common; hyperglycemia, higher levels of systemic

proinflammatory cytokines and oxidative stress (Başoğlu *et al.*, 1999; Giacco, Brownlee, 2010; Pickup, 2004). A systematic review of thirteen observational studies assessing the association of DM and TB showed that DM increases the three-fold risk of getting TB (Jeon, Murray, 2008). Many studies have shown that DM is one of the major risk factors for TB and it may affect the disease progression and outcome of treatment (Chang *et al.*, 2011). Also, it may worsen glycemic control and induce glucose intolerance among DM patients (Restrepo, 2016). A study conducted in Haryana, India reported that the chances of death among TB patients are high, in the case of underlying DM (Pal *et al.*, 2016). Similarly, the chance of re-infection is also high in the case of this co-morbidity (Pal *et al.*, 2016). Apart from that, the immunocompromised DM patients often fail to develop an immunologic response through phagocytosis to attain a minimum level of defense against MDR-TB (Pal *et al.*, 2016). Although the co-morbidity has been studied in detail, there still exist unanswered questions on their mutual interactions and their impact on overall health and treatment outcomes of both diseases (Pal *et al.*, 2016).

PATHOPHYSIOLOGY OF DIABETES – TUBERCULOSIS INTERACTION

TB transmission mainly occurs due to spreads from the breathing of infected air during close contact (Sendi *et al.*, 2008). Although a sputum smear-negative patient can rarely spread TB, more than 80% of the new TB cases result from exposure to a sputum smear-positive cases (Lawn, Zumla, 2011; Zumla *et al.*, 2013) sub-Saharan Africa has been disproportionately affected and accounts for four of every five cases of HIV-associated tuberculosis. In many regions highly endemic for tuberculosis, diagnosis continues to rely on century-old sputum microscopy; there is no vaccine with adequate effectiveness and tuberculosis treatment regimens are protracted and have a risk of toxic effects. Increasing rates of drug-resistant tuberculosis in eastern Europe, Asia, and sub-Saharan Africa now threaten to undermine the gains made by worldwide tuberculosis control programmes. Moreover, our fundamental understanding of the pathogenesis of this disease is inadequate. However, increased investment

has allowed basic science and translational and applied research to produce new data, leading to promising progress in the development of improved tuberculosis diagnostics, biomarkers of disease activity, drugs, and vaccines. The growing scientific momentum must be accompanied by much greater investment and political commitment to meet this huge persisting challenge to public health. There are multiple reasons for the increased predilection for TB in DM patients. The first and most important factor is decreased immunologic response. The immune-depression of DM patients increases their susceptibility to TB infection. DM increases the risk of lower respiratory tract infections (LRTIs) due to impaired cell-mediated immunity and dysfunction of neutrophils (Joshi *et al.*, 1999).

Along with immune deficiency, the high virulence of pathogenic bacteria in an atmosphere of elevated glucose concentration, make DM patients vulnerable to TB infection (Davies, 2005). Therefore, improving the blood glucose control helps to get back the immunity and thereby reduces the chance of infections (Joshi *et al.*, 1999). Malnutrition and physical inertness during TB infection cause increased secretion of adrenaline, cortisol and glucagon at the same time, thereby increasing blood glucose levels (Jick *et al.*, 2006; Kibirige, 2014) and the risk of tuberculosis". Similarly, chronic pancreatitis patients with a higher incidence of TB explain the risk of impaired glucose metabolism and DM (Sullivan, Ben Amor, 2012; Mathieu *et al.*, 2005; Zhan, Jiang, 2015; Tatar *et al.*, 2009).

CO-MORBID CLINICAL MANIFESTATIONS OF DIABETES-TUBERCULOSIS

Patients with TB-DM have worse clinical features compared to patients with individual diseases with more than usual symptoms such as weight loss, fever, dyspnoea, night sweats, delayed recovery of hemoglobin levels, and reduced body mass (Faurholt-Jepsen *et al.*, 2012). Generally, DM patients who are co-infected with TB are elderly and most of them have a history of hypertension and/or obesity (Ogbera *et al.*, 2015). Radiological studies have shown that there is more involvement of parietal pleura in diabetic TB (Pizzol *et al.*, 2016). The multilobar spread of infection and extensive lesions are other features of this condition. These

lesions are usually of merging or flowing type. However, in non-diabetic patients, TB usually affects upper lobes with cavity lesions pulmonary infiltrate and cause paratracheal or hilar lymphadenopathy (Badowski, Perez, 2016; Perez-Guzman *et al.*, 2000; Alavi *et al.*, 2014) clinical and para clinical aspects of pulmonary. Few other symptoms like fatigue, lethargy, fever, anorexia, and weight loss are common in both diabetic and non-diabetic patients with TB. Healthcare practitioners usually suggest a DM patient with these symptoms to get screened for TB, especially when the patient has reduced glycemic control (Pizzol *et al.*, 2016).

USE OF METFORMIN AS ANTITUBERCULOSIS THERAPY

Metformin is one of the most prescribed anti-diabetic drugs worldwide. American Diabetes Association (ADA) suggested that all doctors should prescribe Metformin to their newly diagnosed type 2 diabetes patients (Gebel, 2010). It is inexpensive and is well tolerated (Restrepo, 2016). It specifically reduces hepatic gluconeogenesis without promoting insulin secretion. Therefore it does not cause hypoglycemia and weight gain, unlike other anti-diabetic drugs (Madiraju *et al.*, 2014). However, Metformin increases the risk of developing lactic acidosis. Therefore it should be used cautiously in patients with altered renal and liver function (Restrepo, 2016). Metformin has an anti-inflammatory action and reduces

inflammation by stimulating the formation of T regulatory and CD8 memory T cells along with anti-inflammatory M2 macrophages (Pearce *et al.*, 2009; Yin *et al.*, 2015) CD8 T cells, which have a crucial role in immunity to infection and cancer, are maintained in constant numbers, but on antigen stimulation undergo a developmental program characterized by distinct phases encompassing the expansion and then contraction of antigen-specific effector. These help in the destruction of intracellular *Mtb*. A study illustrates the immunomodulatory effect of Metformin on TB (Singhal *et al.*, 2014). These findings led epidemiologists to examine the effect of Metformin on TB comprehensively.

Recently, the concept of host-directed or host-targeted therapy (HDT) for TB has the gained attention of epidemiologists. HDT for TB helps to shorten the duration of treatment of drug-sensitive TB and to improve the treatment outcome in MDR-TB by preserving the normal lung composition (Sachan *et al.*, 2016). A team of international scientists from Singapore confirmed that the use of Metformin was significantly associated with improved TB control and decreased disease severity. This anti-diabetic drug is, therefore, a promising adjunctive therapy that could enhance the effectiveness of existing TB treatments. Table I shows the various studies supporting the use of Metformin in the prevention and treatment of TB, especially in DM patients.

TABLE I - Studies on the effect of Metformin in tuberculosis patients

Sl.No.	Author, Year	Study title	Method	Key findings
1.	Zhang M, He JQ, 2020	Impacts of metformin on tuberculosis incidence and clinical outcomes in patients with diabetes: a systematic review and meta-analysis.	Systematic review and meta-analysis of 17 observational studies (n=382,828)	Metformin significantly reduced active TB incidence and mortality in DM patients
2.	Yu <i>et al.</i> , 2019	Impact of metformin on the risk and treatment outcomes of tuberculosis in diabetics: a systematic review	Systematic review with 12 observational studies (n=6980 cases)	Metformin significantly reduced TB risk and improved treatment outcomes of TB in DM patients

TABLE I - Studies on the effect of Metformin in tuberculosis patients

Sl.No.	Author, Year	Study title	Method	Key findings
3.	Park <i>et al.</i> , 2019	Metformin and tuberculosis risk in elderly patients with diabetes mellitus	Retrospective cohort study from the National Health Insurance Service-Senior database, South Korea (n=25,164)	Metformin use was associated with a decreased TB risk than sulfonylurea use in elderly DM patients
4.	Lachmandas <i>et al.</i> , 2019	Metformin alters human host responses to <i>Mycobacterium tuberculosis</i> in healthy subjects	In vitro and in vivo studies on effects of metformin in Dutch adults (n=11)	Metformin ameliorates the pathological inflammatory responses associated with TB while enhancing antimycobacterial processes such as ROS production and phagocytosis in humans.
5.	Lee <i>et al.</i> , 2019	Impact of metformin use among tuberculosis close contacts with diabetes mellitus in a nationwide cohort study	National wide cohort study in Taiwan (n=5846)	Metformin use is associated with a lower risk of active TB among TB close contacts with DM, especially for insulin users
6.	Pan <i>et al.</i> , 2018	The risk of TB in patients with type 2 diabetes initiating metformin vs sulfonylurea treatment.	Retrospective cohort study from the Taiwan National Health Insurance Research Database (n= 40,179)	Metformin use in the initial 2 years was associated with a decreased TB risk and metformin users had a reduced risk than sulfonylurea users
7.	Degner <i>et al.</i> , 2018	Metformin use reverses the increased mortality associated with diabetes mellitus during tuberculosis treatment	Retrospective cohort study (n= 2416) from National Taiwan University Hospital	Metformin use associated with significantly reduced mortality during TB treatment
8.	Lee <i>et al.</i> , 2018	The effect of metformin on culture conversion in tuberculosis patients with diabetes mellitus	Retrospective cohort study (n= 499) from Seoul Metropolitan Government Seoul National University Boramae Medical Center and Seoul National University Hospital, South Korea	Metformin improved the sputum culture conversion rate in patients with cavitory pulmonary TB, who have higher bacterial loads
9.	Lin <i>et al.</i> , 2018	Metformin is associated with a lower risk of active tuberculosis in patients with type 2 diabetes	Nationwide population-based cohort study using the Taiwan Longitudinal Health Insurance Database (n= 49,028)	Metformin is associated with a decreased risk of active TB in the DM population
10.	Ma, <i>et al.</i> , 2018	Metformin reduces the relapse rate of tuberculosis patients with diabetes mellitus: experiences from 3-year follow-up	Retrospective cohort study (n=58) in China	Metformin use as a combination drug with existing regimen improved the success rate of ATT and reduced the relapse rate in TB patients with DM

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11.	Marupuru, <i>et al.</i> , 2017	Protective effect of metformin against tuberculosis infections in diabetic patients: an observational study of South Indian tertiary healthcare facility	Case-control study (n=451) IN India	The protective effect of metformin against TB was 3.9-fold than other antidiabetic agents in DM patients
12.	Singhal <i>et al.</i> , 2014	Metformin as adjunct antituberculosis therapy	Preclinical study with mouse model and a retrospective cohort study (n=493) in Singapore	Metformin use was associated with improved control of TB infection and decreased disease severity

ROS: Reactive oxygen species; TB: Tuberculosis
ATT: Anti-tubercular treatment; DM: Diabetes Mellitus;

The action of Metformin on *Mycobacterium tuberculosis*

A decade ago, Guitierrez *et al.*, showed that initiation of the process of autophagy of Mtb-infected macrophages, by any means (physiological, immunological, or pharmacological) could kill Mtb (Gupta, Misra, Deretic, 2016; Gutierrez *et al.*, 2004). "Autophagy is an immune mechanism that controls inflammation and acts as a cell-autonomous defense against intracellular microbes, including Mtb" (Deretic, 2014). Metformin has proved to promote autophagy in macrophages, phagocytosis, phagolysosome and thereby help in the killing of TB bacterium (Singhal *et al.*, 2014).

A study conducted by Singhal *et al.* showed that Metformin enhances both protective and pathological immunity and by enhancing TB host-specific immunity, reducing disease severity and improving treatment outcomes (Marupuru *et al.*, 2017). Metformin can restrict the growth of Mycobacteria through the induction of mitochondrial production of reactive oxygen species (ROS) with the help of activated protein kinase (AMPK) activation (Singhal *et al.*, 2014). While insulin may favor the proliferation of bacteria, when used with Metformin, it alters the production of butyrate (the substance which endorses the growth

of bacteria) and thereby inhibits the Mycobacterial growth (Maniar *et al.*, 2017). Similarly, Metformin also inhibits mitochondrial complex 1 and this leads to the suppression of energy production, which is required for the growth of bacteria (Maniar *et al.*, 2017). Metformin has an anti-folate effect and this helps to inhibit the folate cycle of bacteria. The study also claimed that this drug facilitates the expansion of Mtb-specific IFN secreting CD8+ T cells in uninfected mice which proved that Metformin has an impact on the immune cells of the lungs (Marupuru, *et al.*, 2017). Cytotoxic T cells and CD4+ cells in human control MDR-TB (Singhal, *et al.*, 2014). The study showed that TB patients treated with Metformin have fewer numbers of pulmonary cavities and they were less likely to die as compared to those who were not treated with Metformin. These suggest that Metformin can be recognized as an effective drug to treat active TB along with the standard line of antibiotics (Marupuru *et al.*, 2017). Besides, Metformin also regulates inflammatory responses in the gut with the help of Metformin down-regulated p38 mitogen-activated protein kinase (MAPK) and thereby inhibiting interleukin-6 expression (Di Fusco *et al.*, 2018).

Antibiotic targets and inhibits mycolic acid biosynthesis. Systems-level changes attribute to the decreased flux carrying ability of glycolysis as well as the

citric acid cycle. Metformin targets NDH-I and promotes the rerouting of metabolic fluxes via the de novo NAD biosynthesis pathway and electron transport.

Figure 1 shows the effect of Metformin while using along with anti-TB drugs. Metformin, via nicotinamide adenine dinucleotide (NAD) de novo biosynthesis pathway, reroute metabolic flux. Consequently, it

reduces the process of glycolysis and citric acid cycle in the pathogens. Besides this, systems-level changes and consequent inhibition of mycolic acid synthesis by mycobacterium occurs. Usually, anti-TB drugs target mycolic acid biosynthesis and the combination of Metformin with these drugs favors this mechanism (Vashisht, Brahmachari, 2015).

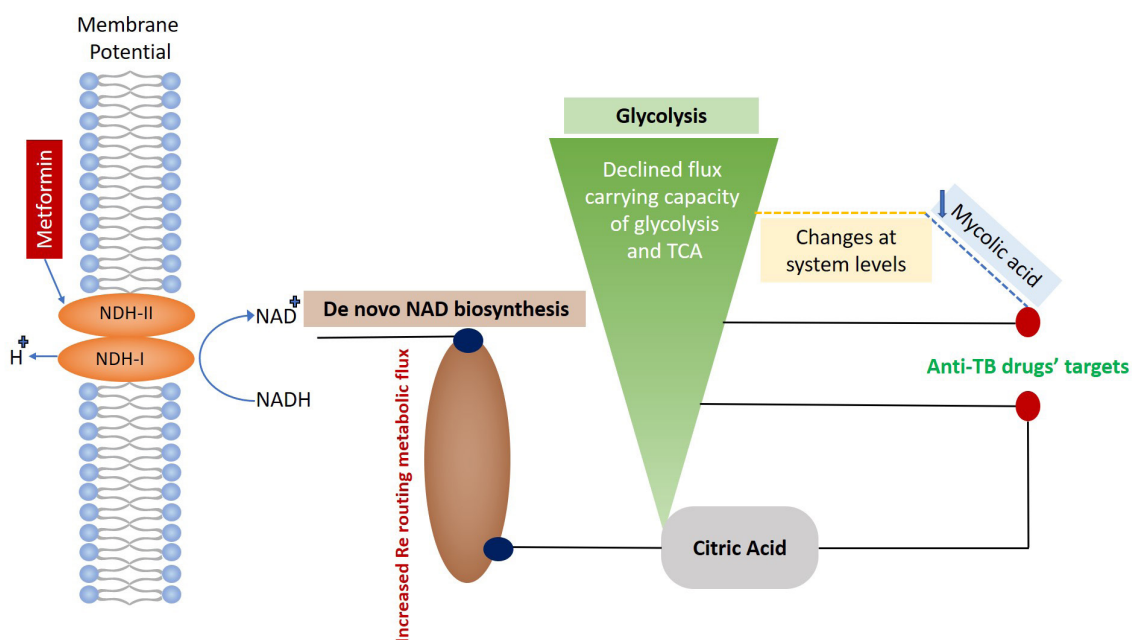


FIGURE 1 - Concept adapted and modified from Vashisht R, Brahmachari SK. Metformin as a potential combination therapy.

with existing front-line antibiotics for Tuberculosis. *J Transl Med.* 2015; 13:83.

The benefits of Metformin to use as adjuvant therapy against TB infections have a great scope; however, these need further investigation. Metformin treatment enhanced the effectiveness of first-line anti-TB drug Isoniazid (INH) and there was a decreased bacterial load in mice treated with both Metformin with INH compared to the mice treated with INH alone (Singhal *et al.*, 2014). When tested with a combination of Metformin with second-line anti-TB drug Ethionamide (ETH) also showed the decreased bacillary load in the lungs and spleen compared to those mice received ETH alone (Singhal *et al.*, 2014).

To improve the effectiveness of TB treatment, anti-Mtb drugs should promote tissue resolution in addition to speeding up bacterial clearance (Zumla, Nahid, Cole, 2013). The involvement of pathogenic changes in the lungs and spleen of TB infected mice treated with Metformin was small as compared to the mice not treated with Metformin (Singhal *et al.*, 2014). Metformin treated Mtb infected mice were found to have more CD4⁺ and CD8⁺ T cells as compared to untreated mice (Singhal *et al.*, 2014). Singhal also identified that there was a reduction in the number of acid-fast bacilli (AFB) and increased lymphocyte infiltration towards infected sites among Metformin treated mice. These evidence showed that Metformin could reduce the pathological changes in Mtb infected tissues. Singhal *et al.* (2014) study also reported

that the DM patients with latent TB taking Metformin had a greater number of IFN-gamma secreting cells against Mtb as compared to the others who are not on Metformin therapy. Another study showed that Metformin amplified the immunity against Mtb by enhancing the development of memory T-cell responses and thereby helped to reduce the incidence of latent TB (Pearce *et al.*, 2009).

Although evidence encourages the use of Metformin in TB patients, caution should be exercised while prescribing the drug in such patients. The possible adverse effects of Metformin in patients with TB comprise of gastrointestinal disorders and very rarely lactic acidosis. Moreover, concurrent use of Metformin and Rifampicin may elevate plasma levels of Metformin and enhance the glucose-lowering effects of the Metformin (Riza *et al.*, 2014). This involves enhanced expression of organic cation transporters (OCT1) and hepatic uptake of Metformin, subsequently leading to an increased glucose-lowering effect. Besides, concomitant use of second-line anti-tubercular treatment (ATT) drugs such as Fluoroquinolones and Linezolid with Metformin may result in hypoglycemia (IBM Micromedex®, 2020). In addition, chronic use of Metformin and ATT in TB patients increases the chance of Vitamin B12 deficiency (Line *et al.*, 1971).

CONCLUSION

Currently, available evidence shows that Metformin has great potential to use as adjunctive therapy for TB. The beneficial effect of Metformin is linked with reducing the inflammatory responses associated with immune pathology and enhancing the anti-mycobacterial activity of immune cells. Further studies are warranted to confirm its comparative effectiveness in both drug-sensitive and drug-resistant TB patients. Additionally, pharmacogenomics studies will help to develop a precision and personalized therapy approach with Metformin to select a suitable candidate for such therapies.

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CONFLICT OF INTEREST

None declared

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