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Protective effect of metformin against tuberculosis infections in diabetic patients: an observational study of south Indian tertiary healthcare facility

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ABSTRACT

Background: World Health Organization estimated that people with diabetes (DM) are at 2–3 times higher risk for tuberculosis (TB). Studies have shown that DM not only increases the risk of active TB, but also puts co-affected persons at increased risk of poor outcomes.
Objectives: To determine the protective effect of metformin against TB in DM patients and also, to investigate the relationship between poor glycemic control and TB.
Methods: A case–control study was conducted over 8 months, where cases and controls were selected based on the inclusion and exclusion criteria of the study. The diabetics diagnosed with TB were selected as study group (SG = 152) and without TB were as control group (CG = 299). Exposure status of metformin in both groups were analyzed.
Results: The mean (SD) age of both CG and SG were 55.54 ± 11.82 and 52.80 ± 11.75, respectively. Majority of the subjects in the study were males. The mean hospital stay of SG and CG were 7 days and 6 days, respectively. Poor glycemic control (HbA1c > 8) observed in SG (51.7%) vs CG (31.4%). HbA1c value <7 is associated protective factor for TB occurrence [OR = 0.52 (95% CI 0.29–0.93)]. The protective effect of metformin against TB was 3.9-fold in diabetics (OR = 0.256, 0.16–0.40).
Conclusion: Poor glycemic control among diabetics is a risk factor for TB occurrence. The result shows metformin use is a protective agent against TB infection in diabetics. Hence, incorporation of metformin into standard clinical care would offer a therapeutic option for the prevention of TB.

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Introduction

Tuberculosis (TB) is one of the most common infectious diseases causing morbidity and mortality worldwide. Each year, approximately 9.6 million new cases and 1.5 million deaths occur due to TB.[1,2] India has the highest burden of TB.[3] More than 95% of TB deaths happen in resource-poor low and middle income countries. Persons with compromised immune states, such as HIV infection, diabetes, tobacco use, and malnutrition are at a greater risk of progressing from latent to active TB.[2] It is possible that in areas of high prevalence of diabetes, the impact of the DM epidemic on tuberculosis could be as great as that of HIV.

Globally, around 15% of TB cases are estimated to be attributable to DM.[4] The escalation of diabetes prevalence in TB-endemic regions may adversely affect tuberculosis control. The current Indian diabetes scenario could lead to resurgence of TB in endemic regions, especially in urban areas.[5] Diabetic patients with TB have negative treatment outcomes such as delay in sputum culture conversion, increased risk of death during treatment, and TB relapse after successful antitubercular treatment regimen.[2] Diabetic TB patients suffer from higher mortality (7.5%) compared to patients with either TB (1%) or DM (2%) alone.[6] A study from Kerala (Southernmost state of India) demonstrated that diabetics with drug sensitive TB have greater probability of failing first line TB treatment as compared to those without DM.[7,8]

Diabetes is associated with diminished innate and adaptive immune responses which are essential to combat the intracellular proliferation of *Mycobacterium tuberculosis* (*M. tb*). Host cell recognition is diminished in diabetics, resulting in the decline of immune response, which render diabetics more susceptible to bacterial infections. Control of TB comprises various strategies such as case treatment, preventive therapy, and vaccination with BCG.[9] TB prevention and control could be further improved by interventions that counter known risk elements of TB such as diabetes, immune compromise in conditions like HIV.

Currently, there are a number of difficulties in developing new drugs with potential anti-TB effects, especially with therapeutic and prophylactic efficacy against dormant *M. tb* organisms. The current anti-tubercular therapy is long drawn and is associated with drug toxicity and heightened multi-drug resistance. Therapeutic modulation of host cell responses that enhances pathogen eradication is being suggested as a new paradigm in drug discovery. These 'host-targeted' therapeutic strategies are less likely to provoke microbial resistance than targeting pathogens with conventional drugs.

Innate antimicrobial arsenal of the host cell includes reactive oxygen species (ROS) and reactive nitrogen species (RNS), in addition to the phagosomal machinery or autophagy. Autophagy is controlled by mammalian target of rapamycin (mTOR) complex-1 and adenosine monophosphate activated protein kinase (AMPK).[10,11] Singhal et al. demonstrated that AMPK-activation by metformin inhibits intracellular growth of *M. tb*, restricting disease immunopathology, and enhancing the efficacy of conventional anti-TB drugs. Singhal's data suggest that both protective immunity and pathological immunity can be independently modulated by metformin during *M. tb* infection by enhancing *M. tb*-specific host immunity, reducing inflammation, promoting disease resolution, and improving treatment outcomes. At the cellular level, metformin differentially affects immune response and inflammation through different mechanisms. The protective effect is mediated by increased host cell production of mROS and increased acidification of mycobacteriod phagosome. Actually, mROS produced upon mitochondrial recruitment to phagosomes is instrumental in killing of intracellular bacteria by macrophages. The anti-inflammatory effect is mediated by activation of AMPK. Metformin also promotes the expansion of *M. tb* specific IFN-γ-secreting CD8+ T cells in uninfected mice indicating that metformin has an impact on the lung immune cells independently of current infections. These effects are consistent with metformin-induced expansion of CD8+ memory T cells, another known consequence of AMPK activation. Both CD4+ and cytotoxic T cells are key to controlling primary *M. tb* infection in human subjects. Studies by Singhal et al. have also shown an increase in *M. tb*-specific T cells in metformin treated diabetic patients with latent TB. Metformin therapy combined with standard TB treatment regimens has demonstrated beneficial clinical outcomes in active TB.

We hypothesize that metformin, via AMPK-activation, boosts host immunity and thereby protect DM patients from TB. As metformin is the most frequently prescribed oral antidiabetic in clinical practice, and since its mechanism of action, including AMPK activation, is well known, a comprehensive preventive strategy of TB in DM should mandate the use of metformin in all diabetics unless contraindicated.

Materials and methods

This case–control study was conducted in a tertiary care hospital in South-India (Kasturba Hospital (KH), Manipal) for a period of eight months (August 2015 to March 2016). Data of patients admitted during Jan 2011 to Dec 2015 were obtained retrospectively from the Medical Records Department of the hospital. Subjects were identified based on ICD-10 coding for disease classification (Diabetes without complications: E11.9; tuberculosis: A15–A19). Study subjects were divided into study group (SG: 152) and control group (CG: 299). SG consisted of diabetics diagnosed with TB and CG had diabetics without TB. The ratio between case and control was kept as 1:2. The inclusion criteria was age ≥40 years. Patient's anti-diabetic medications (metformin or other anti-diabetics or its combinations) usage status were noted.

We used computerized records for identification of case and controls, assessment of comorbidities, and ascertainment of outcome. Control data were collected from discharge summary and identified newly detected diabetes patients with no history of TB, meeting inclusion criteria. Patients diagnosed with DM before 2011, below 40 years, with tuberculosis were excluded from control group. Both case and control data were from the same hospital, with similar exposure status and at risk of developing similar outcome.

The CRF captured demographic data (age, gender, weight, height, BMI, occupation, and social habits) and clinical details (chief complaints on admission, past medical and medication