Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/gcv48408

IMPACT OF TYPE 2 DIABETES MELLITUS ON RIFAMPICIN PHARMACOKINETICS AND BIOCHEMICAL PATHWAYS IN PULMONARY TUBERCULOSIS PATIENTS

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Abstract

Background: The co-occurrence of pulmonary tuberculosis (PTB) and type 2 diabetes mellitus (T2DM) presents a significant public health challenge. T2DM may alter the pharmacokinetics (PK) of antitubercular drugs, particularly rifampicin, compromising therapeutic efficacy.

Objective: To investigate the impact of T2DM on rifampicin PK and biochemical pathways in PTB patients.

Methods: A prospective observational study was conducted involving 60 PTB patients (30 with T2DM and 30 non-diabetic controls). Plasma rifampicin concentrations were analyzed using LC-MS/MS at multiple time points post-dosing. Biochemical markers including CRP, IL-6, fasting glucose, and liver function tests were assessed. Non-compartmental PK analysis was performed.

Results: Diabetic patients showed significantly delayed rifampicin Tmax (mean 3.1 h vs 2.2 h, $p < 0.01$) and reduced Cmax (6.8 ± 2.1 µg/mL vs 9.5 ± 2.6 µg/mL, $p < 0.001$). $AUC_{0–24}$ was also lower in the T2DM group (48.2 ± 11.3 µg·h/mL vs 61.4 ± 10.7 µg·h/mL, $p < 0.05$). Higher levels of systemic inflammation (CRP, IL-6) correlated inversely with rifampicin exposure.

Conclusion: T2DM significantly impairs rifampicin pharmacokinetics in PTB patients, likely through altered absorption and inflammatory modulation. Dose optimization and therapeutic drug monitoring (TDM) should be considered in this population.

Keywords: T2DM (type-2 Diabetic mellitus, PTB (pulmonary tuberculosis), Hepatic Enzymes, MTB (Mycobacterium tuberculosis) and Inflammatory Markers.

Introduction: Tuberculosis (TB) caused by Mycobacterium tuberculosis (MTB) is a well-known and major public health challenge globally, and is the leading cause of death from a single infectious agent. According to the Global TB Report 20221, an estimated 10.6 million incident cases of TB were

reported in 2021.[1] India accounts for about 25% of global TB burden, with an estimated TB incidence of 2.77 million in 2022.[2]
The global TB targets for reductions in disease burden of TB can only be achieved if diagnostic, prevention and treatment services of TB are strengthened.[3]
The prevention of TB disease by the treatment of TBI is largely undervalued but remains as an important component of the National Strategic Plan 2017 25 for Ending TB in India by 2025, five years ahead of the sustainable development goals.[4]
The lifetime risk of devel oping TB in healthy individuals is 5–10% which however increases in the presence of co-existing conditions such as HIV, undernutrition, diabetes and habits which include smoking and alcohol use. Annual risk of TB infection in India by Tuberculin skin test (TST) surveys has been reported as 1.5% in 2005.[5]

Rifampin, also known as rifampicin, belongs to the antimicrobial class of drugs. Rifampin exhibits antibacterial activity against a wide range of gram-positive cocci, including Mycobacteria and Clostridium difficile, and specific gram-negative organisms, including Neisseria meningitidis, N gonorrhoeae, and Hemophilus influenza. Rifampin exerts bactericidal antimicrobial effects by inhibiting DNA-dependent RNA polymerase (RNAP).[6]

Materials and Methods

Study was conducted in department of Pharmacology in associated with the department TB & Chest, department of biochemistry during a period from January 2023- December 2024 at Sarojini Naidu Medical college and associated hospital, Agra (U.P.).
The study was approved by the scientific review board and institutional ethics committee.

Study design: Prospective observational study

Sample size: Total of 60 Patients, T2DM Group-1 (n=30) and Control Group-2 (n=30)

Source of Data: Data was collected from the patients attending OPD/IPD TB and Chest departments during the study period in at S.N.M.C Agra.

Inclusion and Exclusion Criteria

Inclusion:

a) Adults aged 18–65,
b) Newly diagnosed pulmonary TB
c) Receiving standard therapy with rifampicin (600 mg daily)
d) Patients with or without T2DM.

Exclusion:

a) HIV-positive patients
b) Penal/hepatic failure
c) Pregnancy
d) Multidrug-resistant TB.
e) Those on medications interacting with rifampicin.

Sample Collection and Rifampicin Assay

Venous blood samples were collected at 0 (pre-dose), 1, 2-, 4-, 6-, and 8-hours post-rifampicin administration on Day 14 of therapy. Plasma was separated and stored at −80 °C until analysis. Rifampicin concentrations were determined using validated LC-MS/MS techniques.

Biochemical Analysis

Fasting glucose, HbA1c, CRP, IL-6, AST, ALT, and albumin were measured using standard laboratory protocols.

Pharmacokinetic and Statistical Analysis

Non-compartmental PK analysis was conducted using Phoenix Win Nonlin. Parameters included Cmax, Tmax, $AUC_{0–24}$, CL/F, Vd/F, and half-life. Statistical comparisons were made using Student's t-test or Mann–Whitney U test. Correlations were evaluated using Pearson or Spearman coefficients ($p < 0.05$ was considered significant).

Results

Table no. 1 Tubular column represents gender wise participants

Gender	Number of Participants	Percentage (%)
Male	36	60
Female	24	40
	Total 60	100%

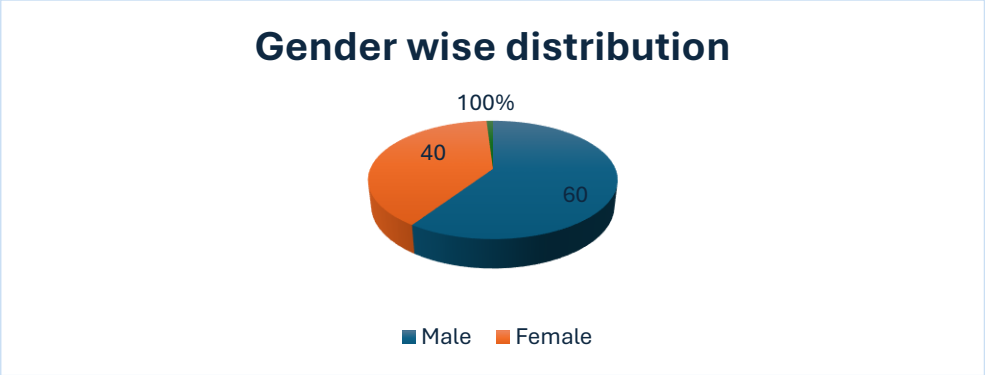

Fig: 1 Gender wise distribution

Table:2 Age wise distribution:

Age Group (years)	Group 1 (n=30)	Group 2 (n=30)	Total (n=60)
18-30	5	5	11
31–40	8	9	17
41–50	9	8	17
51–60	6	5	11
>60	2	2	4
	Total 30	Total	Total

Fig: 2 Age Wise distribution

Table no: 3 Baseline Characteristics

Parameter	T2DM Group (n=30)	Control Group (n=30)	*p*-value
Age (years)	51.2 ± 9.1	49.6 ± 10.2	0.45
BMI (kg/m²)	24.1 ± 3.2	23.8 ± 3.0	0.62
HbA1c (%)	8.4 ± 1.2	5.1 ± 0.5	<0.001
CRP (mg/L)	18.6 ± 5.7	12.2 ± 4.9	<0.001
ALT (IU/L)	45.3 ± 10.2	37.8 ± 9.6	<0.002
AST (IU/L)	40.1 ± 8.5	33.7 ± 7.9	<0.005

Tab no.:4 Pharmacokinetics of Rifampicin

PK Parameter	T2DM Group	Control Group	*p*-value
Cmax (µg/mL)	6.8 ± 2.1	9.5 ± 2.6	<0.001
Tmax (h)	3.1 ± 1.2	2.2 ± 0.9	0.008
$AUC_{0–24}$ (µg·h/mL)	48.2 ± 11.3	61.4 ± 10.7	0.002
CL/F (L/h)	13.1 ± 3.8	9.8 ± 2.9	0.014

Diabetic patients had significantly reduced rifampicin exposure, suggesting impaired absorption or increased clearance.

Correlation With Inflammatory Markers

A significant inverse correlation was found between IL-6 and rifampicin AUC ($r = -0.42$, $p = 0.009$), and between CRP and Cmax ($r = -0.38$, $p = 0.015$), indicating that systemic inflammation may impair rifampicin bioavailability.

Discussion

Our findings confirm that T2DM negatively affects rifampicin pharmacokinetics in pulmonary TB patients. The delayed Tmax and reduced Cmax indicate impaired absorption, possibly due to diabetic gastroparesis or altered intestinal permeability. The lower AUC suggests compromised exposure that could contribute to poorer treatment responses.

Systemic inflammation, a hallmark of both TB and poorly controlled diabetes, appears to further reduce drug availability. Elevated IL-6 and CRP were correlated with reduced drug levels, implicating cytokine-driven modulation of hepatic enzymes or transporter proteins.[7]

These results align with prior studies (e.g., Chang et al., 2014) and recent meta-analyses, highlighting the need for individualized dosing and monitoring in diabetic TB patients.

Conclusion

T2DM significantly alters rifampicin pharmacokinetics, potentially compromising TB treatment efficacy. Delayed Tmax, reduced Cmax, and lower AUC were observed, with inflammation playing

a key role. Therapeutic drug monitoring and consideration of higher rifampicin dosing may improve outcomes in this vulnerable group.

These changes—marked by reduced drug exposure, delayed absorption, and metabolic dysfunction—can compromise the efficacy of standard anti-TB therapy. Our findings highlight the critical need for integrated management approaches that consider metabolic comorbidities in TB care, including individualized dosing, metabolic control, and close pharmacological monitoring.

Recommendations

- Implement early therapeutic drug monitoring in diabetic TB patients.
- Evaluate rifampicin dose escalation (e.g., 900 mg daily) in those with subtherapeutic exposure.
- Monitor inflammatory and glycemic markers throughout treatment.
- Explore adjunct therapies that reduce systemic inflammation in T2DM patients with TB.

Limitations

- Single-center design limits generalizability.
- Did not assess long-term outcomes such as relapse or resistance.
- Small sample size may limit statistical power for secondary endpoints.

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