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Effect of Metformin on Plasma Exposure of Rifampicin, Isoniazid, and Pyrazinamide in Patients on Treatment for Pulmonary Tuberculosis

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Background: To evaluate the effect of metformin on the plasma levels of rifampicin, isoniazid, and pyrazinamide in patients with drug-sensitive pulmonary tuberculosis being treated with first-line antituberculosis treatment (ATT) and to assess the influence of gene polymorphisms on the metabolic pathway of metformin and plasma levels of antitubercular drugs.

Methods: Nondiabetic adults aged 18–60 years with pulmonary tuberculosis were randomized to either the standard ATT (ATT group) or ATT plus metformin (METRIF group) groups in a phase IIB clinical trial. An intensive pharmacokinetic study with blood collection at 0 hour (predosing), followed by 1, 2, 4, 6, 8, and 12 hours after dosing was conducted during the first month of treatment in a subset of 60 study participants after a minimum of 14 doses. Plasma concentrations of rifampicin, isoniazid, pyrazinamide, and metformin were measured by high-performance liquid chromatography using validated methods, and pharmacokinetic parameters and *OCT1* and *MATE1* gene polymorphisms were compared between the groups.

Results: Significant increases in the clearance of rifampicin, isoniazid, and pyrazinamide were observed in patients in the METRIF group (n = 29) compared with those in the ATT group (n = 31). The AA genotypes of the single-nucleotide polymorphism of rs2289669 (*MATE1*) in the METRIF group showed a significantly decreased area under the concentration–time curve to the last observation point and increased clearance of rifampicin.

Conclusions: Metformin altered rifampicin and isoniazid plasma concentrations in patients receiving antituberculosis treatment for pulmonary tuberculosis with little effect on sputum conversion at the end of treatment. Studies with larger sample sizes are needed to understand host drug–drug interactions.

Key Words: host-directed therapy, rifampicin, metformin, sputum culture conversion

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INTRODUCTION

Globally, in 2021, an estimated 10.6 million people fell ill with tuberculosis (TB), and an estimated 1.4 million deaths caused by TB were reported among people without HIV infection.[1] The treatment success rate in adults treated for TB in 2020 was 86%, whereas in children (aged 0–14 years), it was 88%.[1] Although effective regimens are available for treating drug-sensitive TB, the long duration of treatment has posed serious problems to treatment adherence, leading to TB treatment failure and recurrence.[2,3] Moreover, concomitant treatment for coexisting conditions, like diabetes mellitus or HIV infection, may result in drug–drug interactions and affect drug absorption, leading to suboptimal drug levels in plasma.[4,5]

When TB and diabetes mellitus coexist, they should be treated simultaneously. Metformin, along with antituberculosis treatment (ATT), is the most commonly prescribed oral

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antidiabetic agent. Metformin, by facilitating phagocytosis and increasing reactive oxygen species, inhibits the intracellular growth of *Mycobacterium tuberculosis,* thus facilitating early sputum culture conversion when added to ATT.[6–10] As metformin is considered as an adjuvant with ATT for its host-directed effects, it is important to study the pharmacokinetic profiles of anti-TB drugs in the presence of metformin and rule out drug–drug interactions that can impact the treatment outcome. Studies have evaluated the effect of rifampin on metformin pharmacokinetics and its glucose-lowering effect in diabetic patients with TB, with varying results.[11,12] However, no information is available on the pharmacokinetic effect of metformin on first-line anti-TB drugs in nondiabetic patients who do not have diabetes. We evaluated the effect of metformin on the plasma concentrations of rifampicin (RMP), isoniazid (INH), and pyrazinamide (PZA) in patients with drug-sensitive pulmonary TB (PTB) and without diabetes mellitus who received first-line ATT along with metformin as an adjunct host-directed therapy.

MATERIALS AND METHODS

Study Design and Setting

This was a substudy of the metformin plus ATT (METRIF) clinical trial detailed elsewhere.[13] In brief, METRIF clinical trial evaluated the efficacy of metformin when given with ATT in nondiabetic adults with newly diagnosed sputum-positive pulmonary TB on the time to sputum culture conversion. The trial (registered with the Clinical Trial Registry of India CTRI/2018/01/011176) was performed at the ICMR National Institute for Research in Tuberculosis, Chennai, the All India Institute of Medical Science, New Delhi, and the ICMR-National AIDS Research Institute, Pune, where patients to be initiated on ATT were randomized to either the standard ATT [INH, RMP, PZA and ethambutol (EMB)] or ATT plus metformin [INH, RMP, PZA, EMB + metformin-METRIF arm] after obtaining informed written consent. To avoid gastric irritation and vomiting due to metformin, it was administered under supervision at 500 mg once daily for one week followed by 1000 mg daily after food for the remaining 7 weeks of the 8-week intensive phase (IP). Sputum samples were collected weekly to evaluate time-to-culture conversion. This study was approved by the ethics committees of the participating institutes.

Study Procedure

An intensive pharmacokinetic study of 12 hours was conducted in the first month of treatment after the administration of a minimum of 14 doses in a subset of 60 willing study participants who consented to additional blood draws to measure drug levels (29-METRIF group and 31–ATT group). The intensive pharmacokinetics consisted of blood collection at 7 time points over 12 hours, where the 0-hour collection was before the intake of ATT, followed by 1, 2, 4, 6, 8, and 12 hours after drug intake. Two milliliter of blood was collected at each time point in heparinized vacutainers and immediately centrifuged at 2058*g* for 10 minutes. Plasma was separated and stored at −80°C in prelabeled 2.5–5 mL cryovials after adding 5% ascorbic acid to the sample. One milliliter of whole blood was collected from the study participants in a K_2EDTA tube and aliquoted in 2-mL cryovials at the respective study sites at the time of screening for pharmacogenomic analysis. All samples were transported from the study sites to Chennai for pharmacokinetic and pharmacogenomic analyses.

Plasma Drug Levels

Plasma concentrations of RMP, INH, PZA, and MET were estimated using validated methods by high-performance liquid chromatography (HPLC, Shimadzu Corporation, Kyoto, Japan) consisting of 2 pumps (LC-20AD), a photodiode array detector (SPDM20A), and an autosampler (SIL20AC-HT) with a built-in system controller. Briefly, the plasma RMP was extracted using acetonitrile and analyzed using a C18 column at 254 nm. The retention time of RMP was 1.7 minutes.[14] Plasma INH and PZA levels were estimated by extraction with para-hydroxybenzaldehyde and trifluoroacetic acid, respectively. Analysis was performed using a C8 column and detected at a UV wavelength of 267 nm. The retention time of INH and PZA was 6.1 minutes and 3.2 minutes, respectively.[15] The estimation of MET concentrations in plasma involved deproteinization of the sample with methanol, analysis of the supernatant using Zorbax 300—SCX, and UV detection at a wavelength of 233 nm.[16] The methods were validated over the concentration range of 0.25–10.0 mcg/mL for RMP and INH, 1.25–50.0 mcg/mL for PZA, and 0.0625–2.5 mcg/mL for MET and displayed good reproducibility. The percentage recoveries were 95%, 102%, 99%, and 106% for RMP, INH, PZA, and MET, respectively. The between-run and within-run variations for all the drugs were below 10% showing good precision.[14–16]The International Council for Harmonization guidelines were referred for method validation.

Based on the plasma concentrations at different time points, certain pharmacokinetic parameters, including time to attain maximum plasma concentration (T_{max}), maximum plasma concentration (C_{max}), minimum area under concentration (C_{min}), area under the plasma concentration–time curve from time zero to the time of the last quantifiable concentration (AUC_{0-12}), area under the plasma concentration–time curve from time zero to infinity ($AUC_{0-\infty}$), and elimination half-life ($T_{1/2}$) and clearance (Cl) were calculated using the noncompartmental model using the WinNonlin software (Version 8.1) (Pharsight, Certara, Princeton, NJ).

Pharmacogenomics Analysis

DNA was extracted from whole blood using a QIAcube automated nucleic acid extractor (QIAGEN, Germany) and a QIAamp blood DNA mini kit (QIAGEN). DNA purity and quantity were measured using a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific). The entire extracted DNA was diluted to 20 ng/μL concentrations and stored at −20°C. SNPs were determined by direct sequencing or the TaqMan assays. Polymerase chain reaction was performed on the stored DNA samples using specific primers previously published for the SNPs rs594709, rs628031, and rs2289669.[17,18] The amplified products were visualized on 2% agarose gel using a GelDoc XR instrument (Bio-Rad) and purified using ExoSAP IT express purification kit (Thermo Fisher

Scientific). Sequencing was performed using a BigDye Terminator v 3.1 kits (Thermo Fisher Scientific). The sequenced products were run on a 3500 Genetic Analyzer (Thermo Fisher Scientific). SNPs were called using SeqScape software (version 3.0; Applied Biosystems, Foster City, CA). Genotypes were determined for rs622342 using a prevalidated TaqMan assay in a 7500 Fast Real-Time PCR machine (Applied Biosystems), and alleles were called using Applied Biosystems SDS software.

Statistical Analysis

The χ^2 test with one degree of freedom was used to test whether the observed genotypes followed Hardy–Weinberg equilibrium. Data were verified, normality was checked using the Shapiro–Wilk test, and log transformation was performed for non-normal data. The therapeutic ranges (peak concentration) of the drugs administered is RMP: 8–24 mcg/mL; INH: 3–6 mcg/mL; PZA: 20–50 mcg/mL; and MET: 1–2 mcg/mL. Pharmacokinetics (PK) parameters of the 2 treatment groups were compared. The plasma concentrations of RMP, INH, and PZA correlated with patient covariates at baseline, and their bacteriological and clinical end points were evaluated. The Mann–Whitney *U* test was used to compare drug concentrations between the different treatment groups. Statistical *P*-value of ≤0.05 was considered significant. The pharmacokinetic parameters of the observed genotypes were compared to assess the impact of these gene polymorphisms on plasma drug levels, gene–drug interactions, and drug–drug interactions. The pharmacokinetic parameters from 3 or more different genotype groups were compared using the Kruskal–Wallis test in SPSS software version 20.0 (IBM, Armonk, NY).

RESULTS

Of the 60 participants in the PK sub cohort, the majority (80%) were males, the median age was 32.5 years, and the body mass index (BMI) was 18.0 kg/m^2 with a glycosylated hemoglobin level of 5.8% (Table 1). Intensive PK was performed in 31 and 29 patients in the ATT and METRIF groups, respectively. Demographic details of the patients are presented in Table 1. Patients in the METRIF group had a higher BMI than those in the ATT group, both at baseline and during treatment. Because the participants were part of a clinical trial, the drug doses received were as per the weight bands. Gastrointestinal adverse events, including vomiting, were reported at equal frequencies in both the groups.

Pharmacokinetics of Rifampicin and Isoniazid

The pharmacokinetic parameters of RMP, INH, and PZA in both groups are shown in Table 2. Marked interindividual variability was observed in the concentrations of all 3 drugs. Lower RMP plasma concentration was noticed in patients in both groups (4.29 mcg/mL versus 5.29 mcg/mL), whereas INH and PZA plasma concentrations were well within the normal range (Figs. 1A–C). The mean exposure of RMP, INH, and PZA ($AUC_{0-\infty}$) was lower in patients in the METRIF group as compared with those in the ATT group. Similarly, a significant increase in the clearance of RMP, INH, and PZA was observed in patients in the METRIF group compared with those in the ATT group. No significant differences in median C_{min}, T_{max}, or half-life were observed for RMP, INH, and PZA.

Sputum Conversion and Plasma Drug Concentration

Table 3 shows the relationship between the mean plasma exposure to RMP at weeks 4 and 8 and sputum culture conversion. At the end of the 8 weeks of treatment, although not statistically significant, a higher number of patients with positive sputum cultures was observed in the METRIF group (8 versus 3). This group also included more patients with

TABLE 1. Characteristics of Participants in the 2 Arms of the Pharmacokinetic Cohort

Variables	METRIF Group (N = 29) Mean ± SD	ATT Group (N = 31) Mean ± SD	*P*
Age in years	34.3 ± 10.2	30.9 ± 11.5	0.13
No. of males (%)	28 (96.6)	25 (80.6)	0.10
Weight in kg	49.3 ± 6.9	45.0 ± 7.7	0.01
Height in cm	163.0 ± 7.9	160.2 ± 8.4	0.30
BMI at pretreatment	18.5 ± 2.2	17.5 ± 2.8	0.03
At 1st month	18.3 ± 2.1	17.3 ± 2.6	0.02
At 2nd month	18.4 ± 2.1	17.4 ± 2.6	0.03
At 6th month	20.0 ± 2.3	18.6 ± 2.7	0.01
HbA1c at baseline	5.9 ± 0.5	5.7 ± 0.6	0.32
At 2nd month	5.4 ± 0.6	5.4 ± 0.6	0.67
At 6th month	5.5 ± 0.4	5.4 ± 0.4	0.49
Rifampicin (mg)	460.3 ± 68.6	421.0 ± 81.4	—
Isoniazid (mg)	258.6 ± 47.4	229.8 ± 61.0	—
Pyrazinamide (mg)	1246.6 ± 189.8	1159.7 ± 191.3	—
Metformin (mg)	1000.0 ± 00.00		—

Pretreatment (baseline) refers to before the initiation of treatment, whereas the first month refers to 1 month posttreatment.
HbA1c, glycosylated hemoglobin.

TABLE 2. Pharmacokinetic Parameters of Rifampicin, Isoniazid, and Pyrazinamide in Patients on Antituberculosis Drugs With or Without Metformin

	Rifampicin TR: 8–24 (μg/mL)			Isoniazid TR: 3–6 (μg/mL)			Pyrazinamide TR: 20–50 (μg/mL)		
PK Parameter	**METRIF (n = 29) Mean ± SD**	**ATT (n = 31) Mean ± SD**	***P***	**METRIF (n = 29) Mean ± SD**	**ATT (n = 29) Mean ± SD**	***P***	**METRIF (n = 31) Mean ± SD**	**ATT (n = 29) Mean ± SD**	***P***
C_{min}, μg/mL	0.28 ± 0.1	0.28 ± 0.1	0.56	0.22 ± 0.1	0.18 ± 0.1	0.08	0.21 ± 0.7	0.07 ± 0.02	0.42
C_{max}, μg/mL	4.29 ± 2.4	5.29 ± 2.7	0.13	4.24 ± 3.9	4.82 ± 3.2	0.12	37.73 ± 10.4	41.65 ± 10.4	0.09
T_{max} (h)	3.45 ± 1.8	3.61 ± 1.4	0.65	2.38 ± 1.3	2.79 ± 1.7	0.58	3.03 ± 1.4	3.58 ± 1.71	0.23
$AUC_{(0-12)}$ (μg/mL·h)	20.32 ± 9.4	29.83 ± 15.0	0.02	22.70 ± 21.3	27.47 ± 17.7	0.03	323.75 ± 107.1	371.16 ± 100.1	0.09
$AUC_{(0-\infty)}$ (μg/mL·h)	22.82 ± 9.0	33.51 ± 17.7	0.04	29.12 ± 27.5	41.34 ± 33.4	0.02	677.68 ± 300.2	821.15 ± 384.2	0.09
Clearance (mL/min)	23.47 ± 10.6	16.59 ± 9.8	0.002	17.58 ± 15.6	8.31 ± 5.2	0.004	2.19 ± 0.93	1.61 ± 0.51	0.03

C_{max}, maximum concentration; C_{min}, minimum concentration; T_{max}, maximum time for Cmax; TR, therapeutic range.

lower plasma RMP exposure (AUC), suggesting an association between plasma drug exposure and sputum conversion.

Pharmacogenomics and Plasma Drug Levels

Genotype data were available for 55 patients with full pharmacokinetic profiles for both MET and RMP, and these were compared between the genotypes of individuals with *OCT1* (rs628031, rs594709, and rs622342) and *MATE1* (rs2289669) SNPs. Significant differences were observed between ATT and METRIF groups in C_{max} (6.3 versus 4.1 mcg/mL, $P = 0.03$), $AUC_{(0\text{-}12)}$ (40.9 versus 20.5 mcg/mL/h, $P = 0.02$), and RMP clearance (10.8 versus 20.2 mL/min, $P = 0.01$) levels for the AG genotype in the rs628031 SNP of *OCT1*. Similarly, the RMP clearance level (10.8 versus 19.9 mL/min, $P = 0.03$) was significantly higher in the METRIF group for the AG genotype in rs594709 of *OCT1*. Similarly, the AA genotype of the SNP rs2289669 (*MATE1*) in the METRIF group had a significantly decreased $AUC_{(0\text{-}12)}$ (20.3 versus 42.2 mcg/mL·h, $P = 0.03$) and increased clearance of RMP (19.4 versus 10.2 mL/min, $P = 0.02$) compared with the ATT group. Although a difference was observed in the sputum smear conversion rate and mycobacterial growth inhibitor tube positivity at the eighth week of ATT between the genotypes of the 3 SNPs (rs594709 and rs628031 of *OCT1* and rs2289669 of *MATE1*) at the end of the sixth month, the treatment outcomes were similar between the genotypes of all the studied SNPs in both genes and both treatment groups. In addition, no significant differences were observed in the pharmacokinetic parameters of MET in the rs594709 and rs622342 genotypes of *OCT1*, a trend was observed in the C_{max}, $AUC_{(0\text{-}12)}$, and clearance of metformin was observed in the rs628031 (*OCT1*) and rs2289669 (*MATE1*) between the genotypes, but the difference was not statistically significant.

TABLE 3. Correlation Between Plasma Rifampicin Concentration and Sputum Culture Conversion in Participants Treated With Antituberculosis Therapy With or Without Metformin

	No. of Participants with MGIT Culture Result n (%)		
Participants in Study Groups	**Negative**	**Positive**	***P***
At 4th wk of treatment			
ATT arm (n = 31)	12 (38.7)	19 (61.3)	0.951
METRIF arm (n = 29)	11 (37.9)	18 (62.1)	
At 8th wk of treatment			
ATT arm (n = 31)	28 (90.3)	3 (9.7)	0.100
METRIF arm (n = 29)	21 (72.4)	8 (11)	

MGIT, mycobacterial growth inhibitor tube (liquid culture).

DISCUSSION

This study evaluated the effect of metformin coadministration on the pharmacokinetics of INH, RMP, and PZA in nondiabetic patients with PTB, as well as the influence of gene polymorphisms on the metabolic pathway of metformin and plasma levels of antitubercular drugs. We found that exposure to RMP and INH was significantly lower and drug clearance was significantly increased for all 3 drugs in the group that received metformin along with ATT as host-directed therapy.[19] We hypothesize that the lower RMP and INH exposure is the result of a possible pharmacokinetic interaction when metformin is administered with ATT. A study conducted in Indonesia with the primary objective of evaluating the effect of rifampicin on the steady-state pharmacokinetics of metformin showed that rifampicin increased metformin exposure as a result of increased metformin absorption secondary to the upregulation of the transporter gene *OCT1*.[11] However, the above study did not assess the plasma levels of antitubercular drugs; hence, the effect of metformin on anti-TB drugs was not reported.

In our cohort, the number of participants with positive sputum cultures after 8 weeks of treatment was higher in the METRIF group than in the ATT group. The delayed or slow conversion in the METRIF group can be attributed to significant differences in the exposure and clearance of RMP and INH in this group. However, all the patients showed sputum culture conversion at the end of 24 weeks of ATT. Similar to other reports, the low level of the drugs was not associated with the overall treatment outcome of the cure similar to other reports.[20] Also, participants in the METRIF group had higher body weight and were administered higher

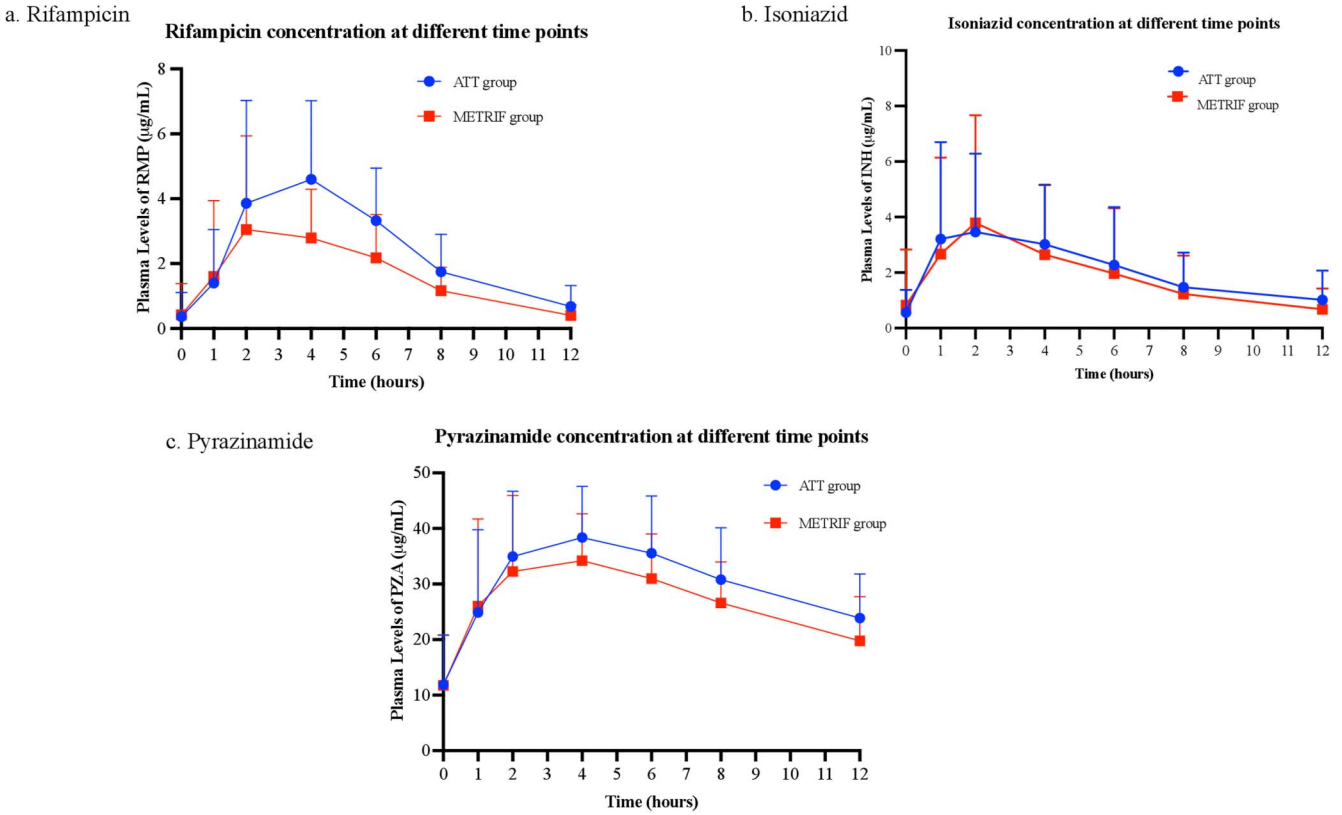

FIGURE 1. A–C, Concentration–time graphs showing the plasma levels of antituberculosis drugs in the study participants in the 2 groups. Data are represented as means + standard deviation (n = 31) in the ATT group and (n = 29) and in the METRIF group.

doses of anti-TB drugs as per the weight band. However, if a patient on ATT does not respond to treatment despite good drug adherence, sensitivity to all drugs, and no vomiting or adverse events, then one can consider increasing the dose of RMP if the plasma drug level is subtherapeutic. In the main clinical trial, participants were randomized using block randomization, and the 2 groups were very similar in terms of body weight, sex, and disease status. In this pharmacokinetic substudy, participants were recruited based on their willingness to draw additional blood samples at multiple time points. This selection of patients may have led to differences in body weight between the 2 groups. We also observed lower $AUC_{0–12}$ and higher clearances of RMP, INH, and PZA in this group. Although the dose of metformin was gradually increased to 1 g, gastrointestinal adverse events were still observed in this group, similar to the TANDEM TB-DM cohort.[11] Treatment in both groups was under direct observation, and the missed doses were also similar; hence, these factors could not be attributed to the difference in PK parameters between the 2 groups.

Association between genetic variation in the *SLC22A1* gene and the blood levels of metformin has been reported in healthy volunteers after an oral glucose tolerance test.[21,22] A study conducted in the South Indian type 2 diabetes mellitus population reported that genotypes of *SLC22A1* rs622342 gene polymorphism were associated with the therapeutic efficacy of metformin.[23] Genetic polymorphisms in *OCT1* *SLC22A1* (rs622342 A>C) and *MATE1* *SLC47A1* (rs2289669 G>A) were associated with metformin uptake, clearance, exposure levels, and therapeutic efficacy.[21,24] Unlike reported studies, we did not observe any significant differences in the metformin levels between the genotypes in the studied SNPs of *OCT1* and *MATE1* genes. The smaller sample size may be a plausible explanation for this finding. From this study, we deduced that metformin is influenced by SNP. Because we did not have a metformin-alone group in our study, we could not ascertain the effect of anti-TB drugs on metformin blood levels.

There was no site-related variability in the pharmacokinetic parameters in our study. The study drugs used at all sites were of the same brand and batch number, thereby eliminating bioequivalence issues. A major limitation of this study was that intensive PK sample collection could only be performed in 60 participants. Host genetic factors related to the pharmacokinetics of antitubercular drugs need to be further evaluated because this study focused only on SNPs relevant for metformin. The difference in the weights of the volunteers between the 2 groups was by chance, which could have affected the clearance of TB drugs in the metformin group. However, the doses of all antitubercular drugs were administered as per weight; we expect that this should have accounted for the differences. The differences in clearance could not be attributed to age or sex because they were similar in both groups.

CONCLUSION

Metformin alters plasma exposure to RMP and INH in patients on treatment for pulmonary TB. Its use as an adjuvant host-directed therapy for TB should be considered in light of its varied effects on pharmacokinetic parameters. Larger pharmacokinetic and pharmacogenetic studies are required to better understand the effects of metformin on the pharmacokinetic parameters of antitubercular drugs.

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