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Brief communication

Can diabetes mellitus modify the plasma concentrations of rifampicin in patients under treatment for tuberculosis?



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ABSTRACT

Rifampicin is a key component of treatment for tuberculosis and its efficacy is determined by the blood levels attained after therapeutic doses. However, there is a high variability of rifampicin blood levels that is related to both the patient and the formulation used. To date, the effect of diabetes mellitus on the plasma levels of rifampicin was low exploited, which could be relevant either by the significant increase of the comorbidity worldwide as by the probable influence of diabetes on the rifampicin exposure. The study aims to evaluate whether diabetes mellitus contribute to the variation of the maximum concentration of rifampicin in patients with tuberculosis treated with a daily dose of 10 mg/kg. Rifampicin and glycated hemoglobin were measured by high-performance liquid chromatography, and blood glucose by spectrophotometry. A total of 62 male patients were included in the study, and 26 presented diabetes mellitus. Rifampicin plasma levels in 2-h plasma samples collected at day 61 ranged from 3 µg/mL to 14.2 µg/mL. Drugs levels were similar between diabetic and non-diabetic patients and were not correlated with blood glucose and glycated hemoglobin. Moreover, a high percentage of patients in both groups presented low levels of rifampicin.

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Tuberculosis (TB) is an important public health issue in Brazil, where approximately 76,000 cases are diagnosed each year.¹ Rifampicin has a potent sterilizing capacity and is used in both phases of treatment for TB.² The therapeutic efficacy of rifampicin is dependent on the relationship between drug susceptibility of *Mycobacterium tuberculosis* and the

achievement of adequate blood concentration of the drug. However, there is a high inter-individual variation in blood rifampicin levels after standard dosages, which can lead to suboptimal concentration, unsuccessful treatment, and emergence of resistance.^{3,4}

In recent years, several studies evaluated the effect of type 2 diabetes mellitus (DM) on rifampicin blood levels.^{5–7} The results were inconclusive, however, with some studies demonstrating significant changes in the pharmacokinetic

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Table 1 – Baseline characteristics of patients.

Characteristic	TB (n = 36)	TBDM (n = 26)	p-value
Age, years	44 (29–56)	38.5 (30–49)	0.1855 ^b
Weight, kg	54 (50–59)	64 (57–70)	0.0046 ^b
Fasting blood glucose, mg/dL	92 (87–96)	186 (121–251)	<0.0001 ^b
Fasting HbA1c, %	5.4 (5.2–5.6)	9.6 (7–12)	<0.001 ^b
HbA1c ≥ 6.5, number of patients	0	26	–
Blood glucose ≥ 126 mg/dL, number of patients	0	25	–
Conversion of sputum smear up 60 days	89 (n = 32)	85 (n = 22)	0.7617 ^a
Dose of rifampicin (mg/kg)	10.14 (9.73–11.08)	9.82 (8.9–10.19)	0.8123 ^b
Plasma rifampicin level below 8 µg/mL, %	75	80	0.6880 ^a

Results are expressed as median and range.

^a Chi-square test.

^b Mann-Whitney *U* test.

parameters of the drug while others revealed a moderate or null influence of type 2 DM on rifampicin disposition. In Brazil, no studies have investigated the blood levels of rifampicin in patients with diabetes and tuberculosis. The current study aimed to evaluate whether type 2 DM contributes to the variation of 2-h plasma concentration of rifampicin in Brazilian patients under treatment for tuberculosis.

The study was carried out between January 2017 and July 2018 in the Health Unit of Guama district, Belem, PA, Brazil. The inclusion criteria were adult male patients (>18 years) with clinical, laboratory, and radiological diagnosis of pulmonary tuberculosis. Exclusion criteria were use of anti-tuberculosis drugs in the last 30 days; HIV, hepatitis A, B, C, or E infection; drug addiction including regular consumption of ethanol and tobacco; hepatic or renal diseases; or history of allergy to the anti-tuberculosis drugs. Patients were allocated into two groups: non-diabetic tuberculosis patients (TB group) and type 2 DM tuberculosis patients (TBDM). Type 2 DM was defined as blood glucose levels above 126 mg/dL and glycated hemoglobin (HbA1c) above 6.5%.⁸

Each patient received a total daily dose of rifampicin (600 mg), isoniazid (300 mg), pyrazinamide (1600 mg), and ethambutol (1100 mg) for two months (intensive phase), and rifampicin (600 mg) plus isoniazid (300 mg) for four months (continuation phase). The drugs were dispensed as a fixed-dose combination in both treatment phases. The continuation phase in patients with DM was extended for additional three months.² The clinical staff of the tuberculosis program from the basic health unit prescribed and dispensed the drugs for free. The first monthly dose was supervised by the research team.

Venous blood samples (4 mL) for analysis of rifampicin, blood glucose, and HbA1c were taken on day 61 at 2 h after drug intake and after 12 h fasting. The samples were centrifuged at 3500 g × 10 min at 4 °C for plasma separation. A fraction of plasma was rapidly processed to determine glucose blood levels and HbA1c. The other fraction was refrigerated at –20 °C for rifampicin analysis.

Glucose blood levels were determined in an Architect 8000 spectrophotometer (Abbott Diagnostics). HbA1c was measured by ion-exchange high-performance liquid chromatography.⁸

Rifampicin was measured by reversed-phase high-performance liquid chromatography using a Flexar[®] system

(Perkin Elmer) after liquid-liquid extraction from plasma, following the procedure proposed by Prasanthi et al., 2015 with modifications.⁹

Qualitative data are presented as frequencies of occurrence and the concentrations of rifampicin in plasma as medians and ranges. The categorical variables were compared between the study groups by the chi-square test. The Mann-Whitney *U* test was used to compare continuous variables. Correlation of rifampicin plasma levels with blood glucose and HbA1c were evaluated using Spearman coefficient. Data were analyzed using SPSS software, Release 21 (IBM Inc, Chicago, IL, EUA). The significance level accepted was 5%.

The research protocol was revised and approved by the Ethical Committee of the Nucleo de Medicina Tropical da Universidade Federal do Pará (Brazil), under the number 2,711,799. All patients provided informed consent at admission to the study.

A total of 62 patients completed the study, 26 (42%) with tuberculosis and fulfilled the criteria for type 2 diabetes mellitus. Only four patients reported the use of hypoglycemic drugs. All patients of the TB group showed glucose blood levels and HbA1c within the normal range and did not report use of hypoglycemic drugs. Although the mean weight was higher among TBDM patients compared to TB patients, both groups received similar mean doses of rifampicin (mg/kg). All patients showed negative sputum smear culture within 180 days, and the percentage of sputum culture conversion within 60 days was lower in the TBDM group. Baseline characteristics of the study patients are listed in Table 1.

The median 2-h plasma concentrations of rifampicin were 6.16 (3.0–14.2) µg/mL and 6.0 (4–8.9) µg/mL in TB and TBDM patients, respectively. The concentrations of rifampicin were similar in both groups of the study ($U = 404$; $p = 0.365$) (Fig. 1). The percentage of patients with rifampicin concentrations ≤ 8.0 µg/mL was 75% and 80% in TB and TBDM groups, respectively. Plasma concentrations of rifampicin were not significantly associated with blood glucose levels in TB ($r_s = -0.155$; $p = 0.366$) and in TBDM ($r_s = -0.280$; $p = 0.353$) groups. A similar result was found for the association of plasma concentrations of rifampicin with HbA1c in TB ($r_s = -0.040$; $p = 0.857$) and in TBDM ($r_s = -0.231$; $p = 0.666$) groups.

The median 2-h plasma concentrations of rifampicin were chosen to compare drug exposure between the groups of

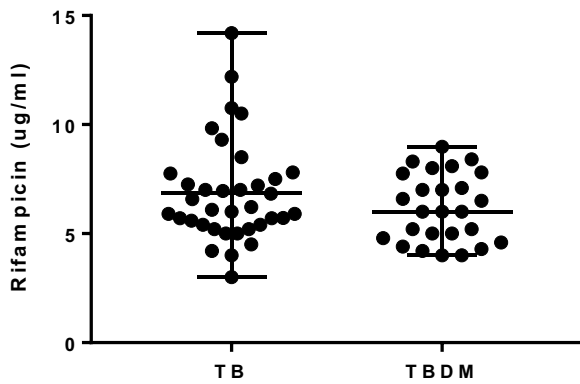


Fig. 1 – Plasma levels of rifampicin in samples collected 2 h after drug intake on day 61 of patients with tuberculosis (TB) and with tuberculosis and type 2 diabetes mellitus (TBDM). The horizontal lines correspond to median and range.

study. Overall, the studies that evaluated the concentrations of rifampicin were performed in samples collected at 2 h after drug intake.^{4,10,11} The mean daily doses of rifampicin given to the patients were similar in both groups and in consonance with the recommendation of the World Health Organization (10 mg/kg).²

A high proportion of patients of both groups showed median 2-h plasma concentrations of rifampicin below the therapeutic target for rifampicin (8 µg/mL). However, the low level of the drug was not associated with treatment outcome, as all patients showed sputum culture conversion after 180 days. Other studies have also shown a high percentage of patients with adequate therapeutic response after 180 days and median 2-h plasma concentrations of rifampicin below 8 µg/mL. The higher percentage of TBDM patients with culture sputum conversion on day 61 is not be considered an adequate predictor of treatment outcome.^{7,12,13} Additionally, there is a probable influence of the immunomodulatory effect of metformin, which increases sputum culture conversion at 60 days.¹⁴

These studies highlighted the importance of attaining target therapeutic concentrations of rifampicin since the drug blood levels are a predictor of treatment outcome.^{7,12,13} Van Ingen et al. (2011) demonstrated that the 600 mg daily dose of rifampicin leads to blood levels above the MIC (0.2 µg/mL) against *M. tuberculosis*, but is at the lower end of the dose–response curve. These authors recommended the use of higher doses of rifampicin to optimize treatment.¹⁵

Diabetes mellitus promotes a negative impact on TB treatment outcomes, as patients can show a higher mycobacterial burden, a longer course for sputum conversion, and a greater risk of treatment failure.^{7,10,11} In this study, most diabetic patients exhibited high levels of blood glucose and HbA1c, revealing poor glycemetic control.

The metabolic effects of DM on the disposition of anti-tuberculosis drugs include impairment of drug metabolism, alteration in duodenal efflux pump P-glycoprotein, and pH in the sites of absorption.^{16,17} In this study, the median 2-h plasma concentrations of rifampicin were similar in both

groups, suggesting that DM has no significant effect on rifampicin exposure; this is supported by the lack of significant correlations of rifampicin plasma levels with both the blood glucose and the HbA1c. These data are in line with a study in Indian patients with tuberculosis, which suggests an increase in the dose or to extend the length of treatment in diabetic patients in order to reach similar exposure levels observed in non-diabetic patients.⁷

The time for blood sampling can be considered a limitation of this study, as 2-h samples could not be the time of maximum drug concentration due to the risk of delayed absorption or malabsorption of rifampicin. However, 2-h samples have been used to assess drug exposure in several studies. Another limitation of the study was the collection of only one blood sample of each patient instead of serial blood samples to estimate the 24-h area-under-the-curve, which could provide a better estimation of the exposure to the drug.^{4,10,11}

In conclusion, the data of the present study suggest that there is no significant effect of diabetes mellitus on the 2-h concentration of rifampicin. Moreover, a high proportion of patients in both groups presented low blood levels of rifampicin. These data contribute to the comprehension of key points related to the use of rifampicin in the treatment for tuberculosis in Brazilian patients.

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Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1. World Health Organization. Global tuberculosis report. Geneva, Switzerland: World Health Organization; 2018.
2. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância das Doenças Transmissíveis. Manual de Recomendações para o Controle da Tuberculose no Brasil. Brasília: Ministério da Saúde; 2019. p. 364.
3. Stott KE, Pertinez H, Sturkenboom MGG, et al. Pharmacokinetics of rifampicin in adult TB patients and healthy volunteers: a systematic review and meta-analysis. *J Antimicrob Chemother.* 2018;73:2305–13.
4. Alsultan A, Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis: an update. *Drugs.* 2014;74:839–54.
5. Babalik A, Ulus IH, Bakirci N, et al. Plasma concentrations of isoniazid and rifampin are decreased in adult pulmonary tuberculosis patients with diabetes mellitus. *Antimicrob Agents Chemother.* 2013;57:5740–2.
6. Verbeeck RK, Gunther G, Kibuule D, Hunter C, Rennie TW. Optimizing treatment outcome of first-line anti-tuberculosis drugs: the role of therapeutic drug monitoring. *Eur J Clin Pharmacol.* 2016;72:905–16.
7. Alfarisi O, Mave V, Gaikwad S, et al. Effect of diabetes mellitus on the pharmacokinetics and pharmacodynamics of tuberculosis treatment. *Antimicrob Agents Chemother.* 2018;62:e01383–1418.
8. Sociedade Brasileira de Diabetes. Atualização sobre hemoglobina (A1C) para avaliação do controle glicêmico e

- para o diagnóstico do diabetes: aspectos clínicos e laboratoriais; 2017. p. 36. Available from: <http://www.diabetes.org.br/publico/images/banners/posicionamento-3-2.pdf>
9. Prasanthi B, Ratna JV, Phani RSCH. Development and validation of RP-HPLC method for simultaneous estimation of rifampicin, isoniazid and pyrazinamide in human plasma. *J Anal Chem.* 2015;70:1015-22.
 10. Fahimi F, Tabarsi P, Kobarfard F, et al. Isoniazid, rifampicin and pyrazinamide plasma concentrations 2 and 6 h post dose in patients with pulmonary tuberculosis. *Int J Tuberc Lung Dis.* 2016;17:1602-6.
 11. Prahl JB, Johansen IS, Cohen AS, Frimodt-Moller N, Andersen AB. Clinical significance of 2 h plasma concentrations of first-line anti-tuberculosis drugs: a prospective observational study. *J Antimicrob Chemother.* 2014;69:2841-7.
 12. Requena-Méndez A, Davies G, Ardrey A, et al. Pharmacokinetics of rifampin in peruvian tuberculosis patients with and without comorbid diabetes or HIV. *Antimicrob Agents Chemother.* 2012;56:2357-63.
 13. Ruslami R, Nijland HM, Adhiarta IG, et al. Pharmacokinetics of antituberculosis drugs in pulmonary tuberculosis patients with type 2 diabetes. *Antimicrob Agents Chemother.* 2010;54:1068-74.
 14. Yu X, Li L, Xia L, et al. Impact of metformin on the risk and treatment outcomes of tuberculosis in diabetics: a systematic review. *BMC Infect Dis.* 2019;19:859.
 15. van Ingen J, Aarnoutse RE, Donald PR, et al. Why do we use 600 mg of rifampicin in tuberculosis treatment? *Clin Infect Dis.* 2011;52:e194-9.
 16. Wang CS, Yang CJ, Chen HC, et al. Impact of type 2 diabetes on manifestations and treatment outcome of pulmonary tuberculosis. *Epidemiol Infect.* 2009;137:203-10.
 17. Restrepo BI, Schlesinger LS. Impact of diabetes on the natural history of tuberculosis. *Diabetes Res Clin Pract.* 2014;106:191-9.