Original Article

The Relationship between Hemoglobin A1C Levels and Sputum Conversion Time in Indonesian Patients with New Cases of Pulmonary Tuberculosis

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Abstract

Background: Hemoglobin A1c (HbA1c) is a glycated form of hemoglobin and is associated with increased susceptibility to tuberculosis (TB), severity, and resistance to therapy. We aimed to determine the impact of HbA1c levels on sputum conversion time among Indonesian patients with pulmonary TB under the intensive phase of TB treatment. **Methods:** This prospective cohort study was conducted in patients with new cases of pulmonary TB patients aged ≥15-year-old and had never been diagnosed with type 2 diabetes mellitus (T2DM). The exclusion criteria of this study are pulmonary TB accompanied by T2DM, pregnancy, or coinfected with human deficiency virus. Statistical analysis was performed using Fisher's exact test to find the relative risk of all variables. We also performed power analysis to check the sample sufficiency. **Results:** One hundred and twenty-three patients of new cases of pulmonary TB were included in this study; of which 63 females and 60 males. There were 12 patients who had HbA1c levels ≥47.5 mmol/mol. More than half (56.1%) of patients had smear-positive acid-fast bacilli and duration of sputum smear conversion time for more than 2 months was recorded in 11 patients (8.9%). There was a significant relationship between HbA1c levels >47.5 mmol/mol and sputum conversion time >2 months with a relative risk of 6.3 (1.9–39.6), value of $P = 0.01$. **Conclusion:** HbA1c levels played an important role toward sputum smear conversion time in patients with new cases of pulmonary TB, and therefore, HbA1c should be considered as an important factor for the outcome in patients receiving anti-TB drugs.

Keywords: Hemoglobin A1c, pulmonary tuberculosis, sputum conversion

Introduction

Tuberculosis (TB) caused by *Mycobacterium tuberculosis* (MTB) is associated with diffuse functional impairment of most endocrine organs resulted in diffuse endocrinopathies.[1] As a chronic infection, TB is also associated with hyperglycemia.[2]

Hemoglobin A1c (HbA1c) is the glycated form of hemoglobin and is regarded as an average level of glucose during the past 90 days.[3-5] The level of HbA1c is closely associated with the prevalence of type 2 diabetes mellitus (T2DM) in various studies. In a prospective study of patients with TB in Southern Mexico, the prevalence of T2DM among 1262 patients with TB was 374 patients (29.63%).[6] Moreover, T2DM with HbA1c >53mmol/mol is related to an increased risk of active pulmonary TB.[7]

The investigation in Indonesia has showed that the proportion of culture conversion at 2 months tends to be similar in patients with T2DM and without T2DM (17.1% and 18.3%), however, when they were reexamined at the end of treatment, the positive cultures were 22.2% in T2DM patients and 9.6% in patients without T2DM.[8] A study by Wijayanto *et al*.[9] revealed that the HbA1c level >8 is associated with TB in T2DM patients. Kulsum *et al*.[10] revealed that an increase in HbA1c level would increase the risk of sputum smear conversion failure 2.313 times greater in patients with T2DM. However, the impact of HbA1c levels in the sputum conversion among Indonesian TB patients who had never been diagnosed with T2DM remains to be elucidated.

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In this study, we evaluated the level of HbA1c in patients with new cases of pulmonary TB and the relationship between HbA1c and sputum conversion.

Methods

This prospective cohort study was conducted in the Indonesian Governmental Respiratory Health Center at Bandung (BBKPM Bandung) from April 2015 to September 2015. The samples were recruited by consecutive sampling. The inclusion criteria were patients with new cases of pulmonary TB, aged ≥15 years and willing to participate in the study by signing a letter of approval. The exclusion criteria were patients who are previously diagnosed with T2DM, pregnancy, and extrapulmonary TB.

This study has granted ethical approval by the Institutional Review Board of the Faculty of Medicine Universitas Indonesia (Ethical Clearance No. 175/UN2.F1//ETIK/2015). Statistical analysis was performed using Fisher's exact test using SPSS software version 21 (IBM Corp, Armonk, New York, USA). A value of $P < 0.05$ was considered to be statistically significant.

We performed power analysis test based on the acceptable statistical assumption ($\alpha = 0.05$, $\beta = 0.2$, and power = 0.8) to ensure we have sufficient sample as described in Figure 1. Using power formula for two group comparisons and statistical corrections for continuity, the calculated minimum total sample size that is required was 54, with minimum allocation in both groups (≥47.5 mmol/mol group and <47.5 mmol/mol group) were 9 and 45, respectively. In the end of the study, we have 69 patients divided into 11 patients of the ≥47.5 mmol/mol group and 58 patients of the <47.5 mmol/mol group. Therefore, using the same formula, the calculated power of our study was 0.85, which above the standard of acceptable statistical assumption.

Results

Initially, there were 130 patients included, but during the subsequent extensive observations, the number of patients got reduced to 123 patients. A total of three patients had died, two patients dropped out and two patients were lost in the follow-up process. There was a nearly equal number of men and women and the mean age was 33.8 + 14.6 years old.

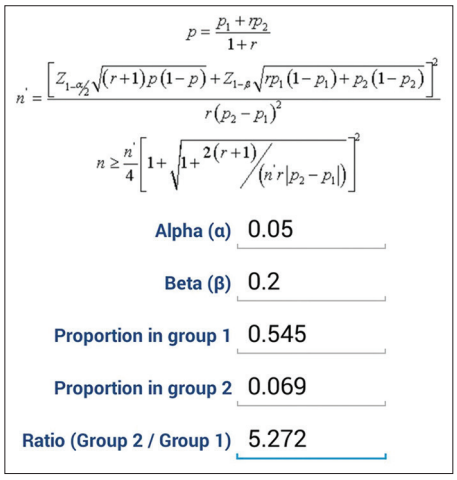

Figure 1: Power analysis for sample sufficiency. Footnotes: Minimum total sample: 54; Minimum sample in group 1: 9; Minimum sample in group 2: 45; Correction for continuity: Yes

In this study, the mean HbA1c level was 42.1 ± 10.53 mmol/mol with a range of HbA1c level from 29.0 to 125.1 mmol/mol. The cutoff point of HbA1c ≥47.5 mmol/mol was used for the classification of T2DM in this study. There were 12 patients (9.8%) with the HbA1c level of ≥47.5 mmol/mol, and therefore, these patients were classified as T2DM. The demographic characteristic of patients, including body mass index (BMI), smoking status, acid-fast bacilli (AFB) status, and time to conversion status, are described in Table 1.

Patients with HbA1c level of ≥47.5 mmol/mol were referred to the Department of Internal Medicine to confirm the diagnosis of T2DM and treatment. A total of 11 patients (8.9%) received metformin therapy, and one patient received insulin therapy. The number of patients who received metformin therapy and had sputum smear conversion occurred within 2 months was five patients (45.5%), while patients with sputum smear conversion >2 months were to six patients (54.5%) and patients who received insulin therapy experienced a conversion of more than 2 months. Nevertheless, the results showed no statistically significant relationship ($P > 0.005$).

First, we determined the relative risk of prolonged sputum conversion time among patients with HbA1c >47.5 mmol/mol as described in Table 2. Most of

Table 1: Characteristic of the subjects

Variable	HbA1c (mmol/ml)	
	<47.5, *n* (%)	>47.5, *n* (%)
Sex		
Male	55 (91.7)	5 (8.3)
Female	56 (88.9)	7 (11.1)
Age		
<34-year-old	73 (98.6)	1 (1.4)
≥34-year-old	38 (77.6)	11 (22.4)
BMI		
<18.5	64 (92.8)	5 (7.2)
18.5-25	47 (88.7)	6 (11.3)
>25	0	1 (100)
Smoking		
Yes	42 (89.4)	5 (10.6)
No	69 (90.8)	7 (9.2)
AFB smear		
Positive	59 (85.5)	10 (14.5)
Negative	52 (96.3)	2 (3.7)
Conversion time of AFB smear (months)		
2	54 (93.1)	4 (6.9)
>2	5 (45.4)	6 (54.5)
Hemoglobin (g/dl)		
<12	50 (86.2)	8 (13.8)
>12	61 (93.8)	4 (6.2)

AFB: Acid-fast bacilli, HbA1c: Hemoglobin A1c, BMI: Body mass index

the smear-positive pulmonary TB patients (93.1%) with HbA1c <47.5 mmol/mol had sputum smear conversion within 2 months, while there were only four (6.9%) patients with HbA1c level ≥47.5 mmol/mol, and had sputum smear conversion time within 2 months. The relative risk of sputum conversion more than 2 months in patients with HbA1c >47.5 mmol/mol was 6.3 (P = 0.01). This implies that HbA1c ≥47.5 mmol/mol would significantly increase the risk of AFB sputum conversion time of more than 2 months by six times compared to patients with HbA1c <47.5 mmol/mol. *Vice versa*, patients with sputum conversion >2 months had significantly (P = 0.0018) higher mean of HbA1c, as shown in Figure 2.

We then analyzed the relationship between bacterial load and sputum conversion time [Table 2]. In this study, a total of 39 patients (31.7%) had bacterial load 1+ (10–99 bacilli/100 field), 19 patients had a (15.4%) result of 2+ (1–10 bacilli/1 field), and 11 patients were (8.9%) categorized in the 3+ (>10 bacilli/1 field). However, there was no statistically significant relationship between bacterial load and sputum smear conversion time (P = 0.736).

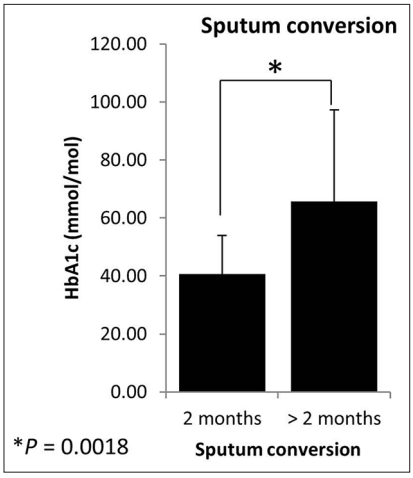

Figure 2: Comparison of means of haemoglobin A1c in tuberculosis patients with sputum conversion of 2 months and >2 months. Footnotes: Statistical analysis was performed by Mann–Whitney test. $P < 0.05$ was considered to be statistically significant

Table 2: The relationship between conversion time, hemoglobin A1c level, and bacterial load

Variables	Conversion time		*P*	RR
	>2 months (%)	2 months (%)		
HbA1c (mmol/mol)				
>47.5	6 (54.5)	5 (45.5)	0.001	6.3
<47.5	4 (6.9)	54 (93.1)		(1.9-39.6)
Bacterial load				
AFB >2+	21 (80.8)	5 (19.2)	0.736	
AFB <2+	37 (86.0)	6 (14.0)		

AFB: Acid-fast bacilli, HbA1c: Hemoglobin A1c, RR: Relative risk

Next, we performed the bivariate analysis to determine the factors that influenced the conversion time in patients with pulmonary TB. The variables considered were the following, sex, age, BMI, smoking habits, AFB status, bacterial load, hemoglobin levels, and HbA1c level. Variables that showed a statistically significant (P = 0.001) only the level of HbA1c with a relative risk of 6.3, meanwhile, other variable showed nonsignificant results using bivariate analysis. This analysis is described in Table 3.

Discussion

Sputum conversion is one of the important outcomes in the treatment of pulmonary TB because it represents the infection control in the environment surrounding TB patients. Identification of factors that may prolong the sputum conversion has been an intensive investigation. In this study, we hypothesized that HbA1c in Indonesian TB patients who had never been diagnosed with T2DM might affect the sputum conversion time.

In this study, number of female patients nearly equal with male patients (51.2% vs 48.8%, respectively). In a previous study by Kulsum *et al*.[10] in the Persahabatan Hospital Indonesia, the new cases of TB patients with diabetes were dominantly male individuals (64.58%). In contrast, Wijayanto *et al*.[9] found new cases of TB patients were more common in women individuals (59.2%) than men (40.8%).[9] Nevertheless, several previous studies have revealed that distribution of the gender is not significantly different.[11-14]

The mean age of patients in this study was 33.8 ± 14.6 years. In contrast to the study conducted by Wang *et al*.[13] their observed the patient's average age was 50.4 ± 18.6 years old. Furthermore, a study by Wijayanto *et al*.[9] had predominantly older age patients (>60 years), as many as 82 patients (49.4%). Similarly, the study by Raghuraman *et al*.[14] had patients ranging from 41 to 50 years of age. In this study, the patients were predominantly teens and young adults. Previous studies, however, included TB patients with confirmed T2DM.

In the current study involving newly diagnosed TB patients, HbA1c level was assessed, and there were 12 patients (9.8%) with HbA1c level ≥47.5 mmol/mol. According to the WHO report in 2011 that stated HbA1c as diagnostic tools for T2DM diagnosis, it can be concluded that the proportion of T2DM in this study is 9.8%.[15] However, in studies by Leung *et al*.[7] and Leegaard, *et al*.,[16] they used the cutoff HbA1c level 53 mmol/mol to diagnose diabetes. The prevalence of T2DM in TB patients is varied across studies. Olayinka *et al*.[12] noted the prevalence of T2DM in TB patients in Nigeria was about 5.7%. T2DM was documented in 14% of 1131 new cases of pulmonary TB in the TB Control Program in South India.[17] Similarly, Alisjahbana *et al*.[8] showed that 94 patients (14.8%) were categorized as T2DM with 57 new patients to have already been diagnosed with T2DM (60.1%). Among 209 TB patients, another study in South India revealed a higher prevalence of T2DM compared to the current study 54.1%, and 3 months of follow-up, the HbA1c declined.[18]

Table 3: The bivariate analysis of factors that affect the sputum conversion time

	2 months conversion (%)	>2 months conversion (%)	*P*	RR
Gender				
Male	27 (84.4)	5 (15.6)	1.0	1.045 (0.2867-3.812)
Female	31 (83.8)	6 (16.2)		
Age				
<34-year-old	33 (86.8)	5 (13.2)	0.525	1.584 (0.434-5.787)
≥34-year-old	25 (80.6)	6 (19.3)		
BMI				
Underweight	37 (84.1)	7 (15.9)	1.000	1.007 (0.264-3.845)
Normal/overweight	21 (84)	4 (16)		
Smoking				
Yes	22 (78.6)	6 (21.4)	0.329	0.473 (0.129-1.739)
No	37 (88.1)	5 (11.9)		
HbA1c (mmol/mol)				
<47.5	54 (93.1)	4 (6.9)	0.001	6.33 (1.571-39.579)
≥47.5	5 (45.5)	6 (54.5)		
Hemoglobin level (g/dl)				
<12	30 (85.7)	5 (14.2)	0.752	1.296 (0.353-4.688)
≥12	28 (82.4)	6 (17.6)		
Bacterial load				
<2+	37 (86.0)	6 (14.0)	0.736	1.468 (0.399-5.398)
≥2+	21 (80.8)	5 (19.2)		

BMI: Body mass index, HbA1c: Hemoglobin A1c, RR: Relative risk

The proportion of patients with smear-positive pulmonary TB was 69 patients (56.1%). In a previous study by Alisjahbana *et al*.,[8] it was found that 29.8% were patients with sputum smear-positive. Wijyanto *et al*.[9] study showed six patients (3.4%) with smear-positive pulmonary TB patients with T2DM and 31 patients (17.8%) with negative sputum smear. Raghuraman *et al*.[14] studied 51 patients (32.9%) with smear-positive TB patients with T2DM. Other study revealed that T2DM patients with HbA1C >53.0 mmol/mol were significantly more likely to be smear-positive as compared to nondiabetic patients.[19] Taken together, there is a tendency of increasing percentage of smear-positive among pulmonary TB patients with T2DM. One of the possible reasons is because patients in this study were patients who have never been diagnosed with T2DM previously while accumulating evidence suggests that T2DM tends to have lesser positivity of bacilli in the microscopic sputum smear.[6,7,11] In a study by Amare *et al*.,[20] the prevalence of sputum smear-positive in TB patients with suspected T2DM was 6.2% and this is lower than the positivity results in our findings.

Regarding bacterial load, we did not find a statistically significant relationship between bacterial load and sputum smear conversion time. Bouti *et al*.[21] studied the factors influencing the sputum conversion time in Morocco; there were 1+ sputum smear on 8 patients (6.7%), 2+ sputum smear in 19 patients (16%), 3+ sputum smear in 37 patients (31.1%), and 4+ sputum smear in 55 patients (46.2%) with approximately 96.6% conversion within 8 weeks. In a study that investigated the factors affecting sputum conversion time among multidrug-resistant TB (MDR TB) cases, Librianty[22] found that bacterial load was significantly associated with prolonged sputum conversion time. Drug-resistant MTB tends to be persisted pathogen that requires more time to be eliminated by the anti-TB drug, and this might explain the different of bacterial load impact on sputum conversion time in drug-resistant TB and drug-sensitive TB.

The implication of T2DM on sputum culture conversion following 2–3 months of anti-TB treatment was varied with relative risks that ranged from 0.79 to 3.25.[23] This study found that TB patients with HbA1c level of ≥47.5 mmol/mol had 6.3 times relative higher risk to sputum conversion time of >2 months compared to patients with HbA1c <47.5 mmol/mol. The result of this study is consistent with the previous study by Kulsum, *et al*.,[10] which concluded that high HbA1c level among T2DM patients will increase (2.313 times) the risk of sputum smear conversion failure. Furthermore, Chaudhry *et al*.[24] and Jiménez-Corona *et al*.[6] found that TB patients with T2DM have a delayed sputum conversion compared to TB without T2DM. A study by Alisjahbana *et al*.[8] found that the proportion of sputum conversion at 2 months tends to be similar in patients with T2DM and without T2DM (17.1% and 18.3%, respectively). Despite all evidence that exists currently, the possible association of T2DM and prolonged sputum conversion remains conflicting. The effect of controlling HbAlc levels by medical intervention in the improvement of sputum conversion time has also not been fully understood, although some studies confirmed that glycemic controls were associated with sputum conversion at 2 months.[25,26] Regarding TB prevention, metformin was significantly associated with reduced risk of TB among T2DM patients.[27]

The bivariate analysis conducted on nine variables showed that HbA1c significantly affected the sputum conversion time. These results are in contrast with the studies by Librianty[22] who identified gender, BMI, bacterial load, second-line treatment history, and resistance patterns, as factors that implicated in the sputum conversion time, although the studies were conducted in MDR TB patients. The similarity of this study with Librianty[22] was in terms of bacterial load factor; the bacterial load ≥2+ will increase the length of time conversion. Moreover, a study by Bouti *et al*.[21] also revealed patients with high smear grading were more likely to have delayed sputum conversion.

The limitation of the present study is that not all potentially confounding factors were confirmed in this study, such as human deficiency virus infection and other chronic inflammatory diseases. This study also limited by a small number of patients and a short period resulting in difficulties for the assessment of the outcome of treatment.

To the best of our knowledge, our study is the first to report a significant relationship between the HbA1c level of ≥47.5 mmol/mol and prolonged sputum conversion time among Indonesian pulmonary TB without a previous diagnosis of T2DM. The measurement of HbA1c level can be used as a tool to diagnose T2DM and to predict the sputum conversion time in new cases of pulmonary TB patients.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Kibirige D. Endocrine dysfunction among adult patients with tuberculosis: An African experience. Indian J Endocrinol Metab 2014;18:288-94.
2. Van Cromphaut SJ, Vanhorebeek I, Van den Berghe G. Glucose metabolism and insulin resistance in sepsis. Curr Pharm Des 2008;14:1887-99.
3. Koenig RJ, Peterson CM, Jones RL, Saudek C, Lehrman M, Cerami A. Correlation of glucose regulation and hemoglobin A1c in diabetes mellitus. N Engl J Med 1976;295:417-20.
4. Miedema K. Standardization of hbA1c and optimal range of monitoring. Scand J Clin Lab Invest Suppl 2005;240:61-72.
5. Peterson KP, Pavlovich JG, Goldstein D, Little R, England J, Peterson CM, *et al.* What is hemoglobin A1c? An analysis of glycated hemoglobins by electrospray ionization mass spectrometry. Clin Chem 1998;44:1951-8.
6. Jiménez-Corona ME, Cruz-Hervert LP, García-García L, Ferreyra-Reyes L, Delgado-Sánchez G, Bobadilla-Del-Valle M, *et al.* Association of diabetes and tuberculosis: Impact on treatment and post-treatment outcomes. Thorax 2013;68:214-20.
7. Leung CC, Lam TH, Chan WM, Yew WW, Ho KS, Leung GM, *et al.* Diabetic control and risk of tuberculosis: A cohort study. Am J Epidemiol 2008;167:1486-94.
8. Alisjahbana B, Sahiratmadja E, Nelwan EJ, Purwa AM, Ahmad Y, Ottenhoff TH, *et al.* The effect of type 2 diabetes mellitus on the presentation and treatment response of pulmonary tuberculosis. Clin Infect Dis 2007;45:428-35.
9. Wijayanto A, Burhan E, Nawas A, Rochsismandoko. Pulmonary tuberculosis in patients with diabetes mellitus type 2. J Respirol Indones 2015;35:1-11.
10. Kulsum ID, Burhan E, Rochsismandoko. Factors affecting sputum conversion in new cases of pulmonary tuberculosis patients new cases with diabetes mellitus. J Respirol Indones 2017;37:109-18.
11. Balakrishnan S, Vijayan S, Nair S, Subramoniapillai J, Mrithyunjayan S, Wilson N, *et al.* High diabetes prevalence among tuberculosis cases in Kerala, India. PLoS One 2012;7:e46502.
12. Olayinka AO, Anthonia O, Yetunde K. Prevalence of diabetes mellitus in persons with tuberculosis in a tertiary health centre in Lagos, Nigeria. Indian J Endocrinol Metab 2013;17:486-9.
13. Wang Q, Ma A, Han X, Zhao S, Cai J, Ma Y, *et al.* Prevalence of type 2 diabetes among newly detected pulmonary tuberculosis patients in China: A community based cohort study. PLoS One 2013;8:e82660.
14. Raghuraman S, Vasudevan KP, Govindarajan S, Chinnakali P, Panigrahi KC. Prevalence of diabetes mellitus among tuberculosis patients in urban Puducherry. N Am J Med Sci 2014;6:30-4.
15. WHO. Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus. Abbreviated Report of a WHO Consultation. Available from: http://www.who.int/diabetes/publications/report-hba1c_2011.pdf. [Last accessed on 2018 Feb 10]
16. Leegaard A, Riis A, Kornum JB, Prahl JB, Thomsen VØ, Sørensen HT, *et al.* Diabetes, glycemic control, and risk of tuberculosis: A population-based case-control study. Diabetes Care 2011;34:2530-5.
17. Banurekha V, Bhatnagar T, Savithri S, Kumar ND, Kangusamy B, Mehendale S, *et al.* Sputum conversion and treatment success among tuberculosis patients with diabetes treated under the tuberculosis control programme in an urban setting in South India. Indian J Community Med 2017;42:180-2.
18. Kornfeld H, West K, Kane K, Kumpatla S, Zacharias RR, Martinez-Balzano C, *et al.* High prevalence and heterogeneity of diabetes in patients with TB in South India: A Report from the effects of diabetes on tuberculosis severity (EDOTS) Study. Chest 2016;149:1501-8.
19. Chiang CY, Bai KJ, Lin HH, Chien ST, Lee JJ, Enarson DA, *et al.* The influence of diabetes, glycemic control, and diabetes-related comorbidities on pulmonary tuberculosis. PLoS One 2015;10:e0121698.
20. Amare H, Gelaw A, Anagaw B, Gelaw B. Smear positive pulmonary tuberculosis among diabetic patients at the dessie referral hospital, Northeast Ethiopia. Infect Dis Poverty 2013;2:6.
21. Bouti K, Aharmim M, Marc K, Sualhi M, Zahrauoui R, Benamor J, *et al.* Factors influencing sputum conversion among smear-positive pulmonary tuberculosis patients in Moroco. ISRN Pulmonol 2013;48:1-6.
22. Librianty N. Factors Influencing Sputum Conversion Time on TB-MDR Patients in Persahabatan Hospital [Thesis]. Jakarta: Universitas Indonesia; 2015.
23. Baker MA, Harries AD, Jeon CY, Hart JE, Kapur A, Lönnroth K, *et al.* The impact of diabetes on tuberculosis treatment outcomes: A systematic review. BMC Med 2011;9:81.
24. Chaudhry LA, Essa EB, Al-Solaiman S, Al-Sindi K. Prevalence of diabetes type-2 & pulmonary tuberculosis among Filipino and treatment outcomes: A surveillance study in the Eastern Saudi Arabia. Inter J Mycobacteriol 2012;1:106-9.
25. Mahishale V, Avuthu S, Patil B, Lolly M, Eti A, Khan S, *et al.* Effect of poor glycemic control in newly diagnosed patients with smear-positive pulmonary tuberculosis and type-2 diabetes mellitus. Iran J Med Sci 2017;42:144-51.
26. Magee MJ, Bloss E, Shin SS, Contreras C, Huaman HA, Ticona JC, *et al.* Clinical characteristics, drug resistance, and treatment outcomes among tuberculosis patients with diabetes in Peru. Int J Infect Dis 2013;17:e404-12.
27. Marupuru S, Senapati P, Pathadka S, Miraj SS, Unnikrishnan MK, Manu MK. Protective effect of metformin against tuberculosis infections in diabetic patients: An observational study of South Indian tertiary healthcare facility. Braz J Infect Dis 2017;21:312-6.