Original Article

Diagnostic Predictors of Active Tuberculosis Infection in Diabetic Patients with Latent Tuberculosis: A Review on Cathelicidin and 1,25-dihydroxyvitamin D_3

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Abstract

Background: Diabetes Mellitus has been identified as one of factors causing increased risks of latent TB infection. The roles of cathelicidin LL-37, 1.25$(OH)_2D_3$ as well as their correlation with specific IFN-γ in latent TB has not been extensively identified. **Aims and Objectives:** Our study was aimed to identify proportion of latent TB infection in patients with DM and to identify the role of cathelicidin, 1.25$(OH)_2D_3$, vitamin D and other clinical factors as predictors for active TB infection in diabetic patients with latent TB. **Methods:** Our study was conducted in 2 stages. The first-stage study was a cross-sectional study to identify the proportion of latent TB infection in patients with DM without any history of TB, which was continued with a case-control study to identify the roles of predictive biomarkers (cathelicidin LL-37, 25$(OH)D_3$, 1.25$(OH)_2D_3$ and IFN-γ) as well as clinical predictive factors for active TB infection in diabetic patients with latent TB. **Results:** Out of 242 diabetic patients without any history of TB who underwent screening test for latent TB, there were 78 (33.2%) subjects with a diagnosis of latent TB and 1 subject was diagnosed with active TB. There was significant association on the level of cathelicidin LL-37 in DM patient with latent TB, active TB and without TB infection (23.49 ng/mL vs. 49.6 ng/mL vs. 10.46 ng/mL, $P < 0{,}005$). Almost all of subjects with DM showed low levels of vitamin D, most in subject with active TB (97%). There was no significant association between 1.25$(OH)2D_3$ and 25$(OH)D_3$ in DM patients with latent TB, active TB and without TB infection. There was a significant association on the levels of IFN-γ ((TB1 1.4 IU/mL vs. 0.03 IU/mL $P < 0.005$; TB2 1.4 IU/mL vs. 0.04 IU/mL $P < 0.005$) in DM subjects with latent TB and those without TB infection; however, no significant association was found in DM subjects with latent TB and active TB. History of smoking, HbA1C > 9.5% and cathelicidin LL-37 levels of > 30 ng/mL were predictors for latent TB into active TB in DM patients. **Conclusion:** Cathelicidin LL-37 can serve as a biomarker of latent TB progressiveness in patients with DM.

Keywords: 1,25 $(OH)_2D_3$, cathelicidin, diabetes, latent tuberculosis infection, Vitamin D

Introduction

Tuberculosis (TB) is a pandemic problem worldwide with an increasing number of patients each year. Primary infection of *Mycobacterium* TB (MTB) will develop into TB disease in 5%–10% individuals and the remaining will have latent TB infection (LTBI).[1,2]

In patients with diabetes mellitus (DM), one of the factors causing an increased risk for LTBI is uncontrolled hyperglycemia conditions that may disrupted the immune system.[3] The disrupted immune system in DM may involve the innate and adaptive immune system that may result in a chain of failures starting from the phagocytosis process by

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the macrophages, cytokines secretion, and decreased levels of Vitamin D.[4]

Vitamin D (25(OH) D_3) has been known to have essential roles in innate and adaptive immunity. It has been identified that $1,25(OH)_2D_3$, an active form of Vitamin D, is a potent inducer of cathelicidin.[5] Cathelicidin is an antimicrobial peptide which has a role in the immunity process against TB.[6] Cathelicidin LL-37 is an extremely potential biomarker for active TB. The roles of cathelicidin LL-37, $1,25(OH)_2D_3$ and their correlation with specific interferon gamma (IFN-γ) have not been widely explored in LTBI and less known in LTBI with DM comorbidity. The aim of our study was to identify the prevalence of LTBI in patients with DM and to identify the roles of cathelicidin, $1,25(OH)_2D_3$, Vitamin D, and other clinical factors, as predictors for active TB in diabetic patients with latent TB.

Methods

The study was conducted in two stages. The first-stage study was a cross-sectional study to identify the proportion of LTBI in patients with DM, which was continued with a case–control study to identify the roles of predictive biomarkers (cathelicidin LL-37, 25(OH) D_3, $1,25(OH)_2D_3$, and IFN-γ) as well as clinical predictive factors for active TB in diabetic patients with LTBI.

The first-stage study was carried out by tracing samples of DM patients who had no history of TB (screening the LTBI) and it was performed at the Outpatient Endocrinology Clinic of Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia, and at the Integrated Outpatient Diabetes Clinic of Persahabatan Hospital, Jakarta, Indonesia, with a total number of 242 patients, while DM patients who had active lung TB infection were traced at the Lung Outpatient Clinic at the Persahabatan Hospital, Pondok Kopi Jakarta Islamic Hospital, Indonesia, and Harapan Jayakarta Hospital, Jakarta, Indonesia, with a total number of 33 patients. Screening for LTBI was performed using interviews on the presence and absence of TB symptoms, history of contact, past medical history of diabetes (duration of having diabetes and controlling diabetes), which were then followed by IFN-γ Release Assay (IGRA) using QuantiFERON-TB Gold Plus (QFT-Plus), chest X-ray, and GeneXpert MTB/Rif assay (Rapid Molecular Test/RMT). Study subjects were divided into three groups: DM with LTBI (DM-LTBI), DM with active pulmonary TB (DM-TB), and DM without TB infection (DM-only) groups. About 34 patients of each group out of the three groups were matched for sex and age groups. The levels of cathelicidin LL-37 were determined using the Human Cathelicidin antimicrobial peptide/LL-37 ELISA kit (MyBioSource). The $1,25(OH)_2D_3$ and $25(OH)D_3$ were examined by the liquid chromatography–mass spectrophotometry detector. The value of TB-specific IFN-γ was obtained from the results of QFT-Plus assay. This study has been approved by the Institutional Review Board of the Faculty of Medicine, Universitas Indonesia.

Bivariate analysis was performed using Kruskal–Wallis test, Mann–Whitney U-test, one-way ANOVA test, and Chi-square test, and multivariate analysis was performed by logistic regression. Statistical analysis was performed in the obtained data using the Statistical Package for the Social Science (SPSS) software program version 20 (IBM Corp, Armonk, NY, USA). $P < 0.05$ was considered to be statistically significant.

Results

Of 242 patients with DM who had no history of TB, we found that their median of age was 59 years and there were a greater number of female patients, as seen in Table 1. Their marital status was married and their occupation was predominantly homemakers. In general, the patients had DM for 10 years with poor control. The values of fasting blood glucose (FBG), 2-h postprandial blood glucose (2 hPP), and hemoglobin A1c (HbA1c) levels are described in Table 2. There were 40.9% of the patients with positive QFT results. There were 82 (33.8%) patients who were diagnosed with LTBI and 1 patient was diagnosed with active pulmonary TB.

In the advanced stage of the study, which was carried out for 102 patients with DM, the patients were categorized into three groups, namely DM-LTBI, DM-TB, and DM-only groups, in which each group consisted of 34 patients with 16 male and 18 female patients [Table 3]. The selection of patients in this stage was initiated by matching the sex and age group of patients with lung TB with patients in latent TB group and those without TB infection, who were selected using simple random sampling technique out of their groups. There was no difference regarding the history of TB contact between DM-LTBI patients and DM-only as well as between DM-LTBI patients and DM-TB patients. There was a significant difference regarding the history of smoking between DM-LTBI and DM-TB. There were a greater number

Table 1: Sociodemographic characteristics of patients undergoing latent tuberculosis and lung tuberculosis screening (*n*=242)

Characteristics of subjects	*n* = 242
Sex	
Male	95 (39.3)*
Female	147 (60.7)
Age (years)	59 (34-82)**
<40	13 (5.4)
40-49	28 (11.6)
50-59	86 (35.5)
≥60	115 (47.5)
Marital status	
Married	203 (83.9)*
Widow/widower	33 (13.6)
Unmarried	6 (2.5)
Occupation	
No work	13 (5.4)*
Homemakers	92 (38.0)
Employee	77 (31.8)
Retired	60 (24.8)

*n (%), **Median (minimum-maximum). TB: Tuberculosis

Table 2: Characteristics of diabetes and risk factors for tuberculosis in patients without history of tuberculosis

Characteristics	*n*=242 (%)
Duration of having diabetes (years)	10.0 (1-38)**
1-5	74 (30.6)*
6-15	96 (39.7)
>15	72 (29.7)
FBG (mg/dL)	138 (71-343)
2hPP (mg/dL)	194.0 (64-457)
HBA1c (%)	7.50 (5.3-13.5)
<7	94 (38.8)
7-9.9	108 (44.6)
≥10	40 (16.6)
Smoking history	
Smoker	24 (9.9)
Non-smoker	173 (71.5)
Ex-smoker	45 (18.6)
History of alcohol consumption	
Yes	3 (1.2)
No	228 (94.2)
Used to	11 (4.5)
BCG vaccination	
Yes	40 (16.6)
No	26 (10.7)
Unclear	176 (72.7)
BCG scar	
Present	135 (55.8)
Absent	107 (44.2)
History of TB contact	
Yes	28 (11.5)
No	133 (55.0)
Unclear	81 (33.5)
TB symptoms	
Yes	27 (11.2)
No	215 (88.8)
BMI	26.34±4.7***
<18.5 (underweight)	5 (2.1)
8.5-22.9 (normal)	69 (28.5)
23.0-24.9 (fat)	65 (26.9)
≥25.0 (obese)	103 (42.5)
IGRA	
Positive	99 (40.9)
Negative	143 (59.1)
IFN-γ	
TB1-Nil	0.14 (0.0-10.0)
TB2-Nil	0.18 (0.0-10.0)
Xpert MTB/Rif	
MTB detected	1 (0.4)
MTB not detected	241 (99.6)

*n (%), **Median (minimum-maximum), ***Mean±SD. FBG: Fasting blood glucose, HBA1c: Hemoglobin A1c, TB: Tuberculosis, SD: Standard deviation, BMI: Body mass index, MTB: *Mycobacterium tuberculosis*, IGRA: Interferon Gamma Release Assay, IFN-γ: Interferon gamma, BCG: Bacillus Calmette-Guerin

of smokers in the DM-TB group compared to the DM-LTBI. However, there was no significant difference in smoking history between DM-LTBI and DM-only. The DM-LTBI group was the group with the longest duration of having diabetes, which was 8.5 years compared to the DM-TB group (3 years) and DM-only (5.5 years); nevertheless, there was no difference on the duration of diabetes between DM-LTBI group and DM-only group. All patients showed poor glycemic control. There was a significant difference in HbA1c level between DM-LTBI patients and DM-only patients. However, there was no significant difference in FBG and 2 hPP glucose levels between DM-LTBI patients and DM-only patients. There were significant differences in HbA1c, FBG, and 2 hPP blood glucose levels between DM-LTBI patients and DM-TB patients. The body mass index (BMI) in DM-TB was found lowest among the three groups. There was a significant difference in BMI between DB-LTBI patients and DM-TB patients but no difference when compared to DM-only patients.

As presented in Table 4, all patients in all the three groups had Vitamin D deficiency. DM-TB patients had the lowest level of Vitamin D; however, there was no significant difference in the levels of Vitamin D 25(OH) D_3 among the three studied groups. The highest level of 1.25($(OH)_2D_3$ was found in the DM-TB group compared to the DM-LTBI and DM-only groups, and there was no significant difference in 1,25$(OH)_2D_3$ levels among the three studied groups. We found a significant difference in the levels of cathelicidin LL-37 between three studied.

The levels of specific IFN-γ, which was measured in the study, derived from T-lymphocytes CD4+ (TB1) and T-lymphocytes CD4+ and CD8+ (TB2). In Table 4, the specific IFN-γ (TB2-Nil) level in DM-only patients was higher compared to the specific IFN-γ (TB1-Nil) level. There was a similar IFN-γ level of TB1-Nil and TB2-Nil in the DM-LTBI group, while in the DM-TB group, the IFN-γ (TB2-Nil) was far higher than IFN-γ (TB1-Nil). There was a significant difference of IFN-γ TB1-Nil and TB2-Nil between DM-LTBI group and DM-only group; however, there was no significant difference between DM-LTBI group and DM-TB group.

Furthermore, we performed multivariate analysis and there were three variables that obviously had significant results on the risk of LTBI developing into active TB [Table 5], which were history of smoking, HbA1c level, and cathelicidin LL-37 level.

To obtain variables that could predict the development of active TB in DM patients with latent TB without being affected by other factors, a logistic regression was performed by including variables that had been modified previously, and therefore, a cutoff value could be obtained for each variable, and we identified that the history of smoking had a significant correlation with the risk for developing active TB in DM patients with latent TB, which was 3.1 folds (adjusted odds ratio [aOR] 3.11; 95% confidence interval [CI]: 1.004–9.648), while HbA1c levels >9.5 had 3.5-fold risk (aOR 3.49; 95% CI: 1.183–10.278) and cathelicidin LL-37 level >30 ng/mL had 3.74 risk for developing active TB (aOR 3.74; 95% CI: 1.253–11.161) [Table 6].

Table 3: Correlation of tuberculosis risk factors in diabetic patients with latent tuberculosis, active tuberculosis, and without tuberculosis infection

Characteristics	DM withoutTB infection (*n*=34), *n* (%)	*P*	DM withlatent TB (*n*=34) (references), *n* (%)	*P*	DM withActive TB (*n*=34), *n* (%)
History of TB contact					
Yes	7 (20.55)	0.086[a]	7 (20.7)	0.10[a]	12 (35.2)
No	20 (58.9)		12 (35.2)		15 (44.1)
Unclear	7 (20.55)		15 (44.1)		7 (20.7)
Smoking history					
Smokers	8 (23.5)	0.20[a]	3 (8.8)	0.04[a]	11 (32.4)
Ex-smokers	7 (20.6)		6 (17.6)		5 (14.7)
Nonsmokers	19 (55.9)		25 (73.5)		18 (52.9)
Duration of DM (years)	5.5 (1-18)		8.5 (1-26)		3 (1-21)
≤5	17 (50.0)	0.32[b]	9 (26.5)	0.005[b]	24 (70.6)
6-15	12 (38.7)		19 (55.9)		8 (23.5)
>15	5 (14.7)		6 (17.6)		2 (5.9)
FBG (mg/dL)	140.5 (84-273)	0.32[b]	140 (82-343)	0.001[b]	229 (94-403)
2hPP (mg/dL)	195.76±58.59	0.131[c]	229.65±77.16	0.00[c]	310.71±82.59
HbA1c (%)	6.9 (5.7-12.9)	0.01[b]	8.45 (5.5-12.5)	0.003[b]	10.35 (6.4-15.7)
<7	18 (52.9)		7 (20.6)		2 (5.9)
7-9.9	10 (29.4)		16 (47.1)		14 (46.7)
≥10	6 (17.6)		11 (32.4)		18 (52.9)
BMI	25.66 (18.31-37.78)	0.28[b]	25.18 (16.22-36)	0.01[b]	23 (15.63-28.44)
<18.5	1 (2.9)		4 (11.8)		4 (11.8)
18.5-22.9	11 (32.4)		10 (29.4)		14 (41.2)
23.0-24.9	5 (14.7)		10 (29.4)		14 (41.2)
≥25.0	17 (50.0)		10 (29.4)		2 (5.9)

Numerical data were presented in mean±SD or median (minimum-maximum). [a]Chi square, [b]Kruskal-Wallis + *Post hoc* Mann-Whitney, [c]One-way ANOVA *post hoc* Tamhane. SD: Standard deviation, BMI: Body mass index, DM: Diabetes mellitus, TB: Tuberculosis

Table 4: Correlation of Vitamin D 25(OH)D_3, 1,25$(OH)_2D_3$, cathelicidin, and interferon-gamma specific in diabetes mellitus subjects with latent tuberculosis, lung tuberculosis and without tuberculosis Infection

Index	DM without TB infection	*P*	DM with latent TB (reference)	*P*	DM with active TB
25$(OH)D_3$ (ng/mL)	18.61±10.92	0.97[a]	17.77±8.53	0.54[a]	15±10.14
Normal	8 (23.5)		3 (8.8)		1 (2.9)
Abnormal	26 (76.5)		31 (91.2)		33 (97.1)
1,25$(OH)_2D_3$ (ng/mL)	43.5±43.5	0.91[b]	51.38±49.31	0.99[b]	53.88±59
Cathelicidin (ng/mL)	10.46 (0.26-78.01)	0.01[b]	23.49 (2.57-53.13)	0.00[b]	49.6 (9.3-174.11)
IFN-γ (IU/L)					
IFN-γ (TB1-Nil)	0.03 (0-0.29)	0.00[b]	1.4 (0.18-7.89)	0.57[b]	1.79 (0.01-10)
IFN-γ (TB2-Nil)	0.04 (0-0.3)	0.00[b]	1.4 (0.22-8.02)	0.10[b]	3.7 (0.06-10)

Numerical data were presented in mean±SD or median (minimum-maximum). [a]One-way ANOVA *Post Hoc* Tamhane, [b]Kruskal-Wallis + *Post hoc* Mann-Whitney. DM: Diabetes mellitus, TB: Tuberculosis, IFN-γ: Interferon gamma, SD: Standard deviation

To calculate the probability of predicting TB latent in DM patients progressing into active TB and to develop a diagnostic algorithm, an additional statistical analysis was carried out. When TB patients with latent TB had a history of smoking (smokers and ex-smokers) alone or with HbA1c level >9.5% alone or with cathelicidin LL-37 level >30 ng/mL alone, the probabilities of developing active TB were 35.3%, 37.9%, and 39.6%, respectively. When there was a combination between the history of smoking and HbA1c level >9.5%, the probability of progression into active TB was 65.6%. The probability would increase when there was a combination factor between the history of smoking, cathelicidin LL-37 level >30 ng mL and a combination between HbA1c level >9.5% and cathelicidin LL-37 of >30 ng/mL up to 67.1% and 69.6%, respectively. The probability of developing into active TB would further increase up to 87.7% when the three factors in DM patients with latent TB coexisted, i.e., the history of smoking, HbA1c level >9.5%, and cathelicidin LL-37 level >30 ng/mL.

Discussion

In this study, we identified the prevalence of LTBI in patients with DM and determined the roles of cathelicidin, 1,25$(OH)_2D_3$,

Table 5: Results of logistic regression multivariate analysis on predictor factors of diabetes mellitus with latent tuberculosis progressing into active tuberculosis

Parameters	Koefisien	SE	*P*	OR	95% CI
History of smoking	−0.828	0.392	0.034	0.437	0.203-0.941
HbA1c	−0.984	0.469	0.036	0.374	0.149-0.936
Cathelicidin LL-37	0.051	0.016	0.002	1.052	1.019-1.087
Konstanta	1.820	1.261	0.149	6.170	

HbA1c: Hemoglobin A1c, SE: Standard error, OR: Odds ratio, CI: Confidence interval

Table 6: Adjusted odds ratio for predictor variables of active tuberculosis in diabetes mellitus with latent tuberculosis

Variables	*B*	SE	*P*	AOR	95% CI
Smoker	1.135	0.577	0.049	3.113	1.004-9.648
HbA1c >9.5%	1.249	0.551	0.024	3.487	1.183-10.278
Cathelicidin LL-37 >30 ng/mL	1.319	0.558	0.018	3.740	1.253-11.161

SE: Standard error, CI: Confidence interval, AOR: Adjusted odds ratio, HbA1c: Hemoglobin A1c

Vitamin D, and other clinical factors, as predictors for active TB in diabetic patients with latent TB.

Our results on the prevalence of latent TB in DM patients are similar with the results obtained by Koesoemadinata *et al*.,[7] at the Hasan Sadikin Hospital in Bandung, Indonesia, in which the prevalence of LTBI among DM patients without any history of TB was 38.9%, while for active lung TB, it was 3.7%. Leow *et al*.[8] also found only 1 patient with active lung TB out of 220 DM patients who were screened for TB.

Swarna Nantha *et al*.[9] found that the duration of diabetes in DM patients with LTBI was 9.5 years, which is not far too different from the results of our study. A study by Merza *et al*.[10] found a significant association between the duration of having diabetes of ≥10 years with latent TB (odds ratio 2.692; 95% CI: 1.016–7.267).

A previous study showed that DM patients with FBG level of >130 mg/dL have 2.6-fold risk for developing latent TB compared to patients without any history of diabetes.[11] Furthermore, Martinez *et al*.[12] in their study found that the mean HbA1c level in diabetic patients with LTBI was 7.5%. The value is lower compared to the results of our study and there was a significant difference in HbA1c level among the groups of DM-LTBI, DM-only, and DM-TB. Martinez *et al*.[12] in their study have demonstrated that HbA1c levels of ≥7% increase the risk of developing latent TB.

It has been known that smoking has a clear association with increased risk of TB infection, active TB, recurrence during TB treatment session, and death caused by TB. Smoking disrupted clearance of airway secretion, disrupted function of lung macrophages, and reduced production of IFN-γ and TNF-α. Previous study had demonstrated that smoking increases the risk for TB infection as great as 1.83 folds (95% CI: 1.49–2.23) and increases the risk for developing active TB as many as 2.29 folds (95% CI: 1.93–2.71).[13]

All the study groups have demonstrated a Vitamin D deficiency (<20 ng/mL). The low Vitamin D level in patients with pulmonary TB may also due to low expression of mRNA for Vitamin D-binding protein, which is consistent with the low albumin level in patients with active TB compared to healthy control and those with household contacts of TB.[14] *In vitro* and *in vivo* studies have demonstrated that Vitamin D is extremely essential for insulin secretion as a response to glucose and in maintaining glucose tolerance.[15]

Currently, there are no data about $1,25(OH)_2D_3$ expression on DM patients with TB infection. Low $1,25(OH)_2D_3$ level causes reduced phagocytosis capacity of the macrophages; therefore, it may become a predisposition for TB infection and a risk factor for developing active TB.[16] Abnormal Vitamin D metabolism has been widely observed in infection. During infection, the increased level of active $1,25(OH)_2D_3$ will reduce Vitamin D $25(OH)D_3$ level due to increased Vitamin D breakdown. It has been reported that Vitamin D deficiency is associated with the risk of developing Type 2 DM.[17]

There was a statistically significant difference in cathelicidin LL-37 levels between the DM-LTBI group and the DM-only group as well as the DM-TB group. Antimicrobial protein such as cathelicidin LL-37 is an important component of innate immunity against the pathogen, which is expressed primarily from the immune cells and plays a role on antimicrobacterial macrophages activities. It explains the increased cathelicidin levels in active TB compared to LTBI and normal patients.[18,19] In our patients, the higher level of cathelicidin LL-37 in DM-LTBI patients compared to DM-only patients, but lower level than DM-TB, indicates that there is an ongoing process of MTB multiplication or ongoing inflammatory process.[19,20]

The measurement of specific IFN-γ from CD8+ is an interesting additional feature from QFT plus, which is different from the previous generation of QFT. A study by Lee *et al*.[21] showed that the CD8+ response in QFT Plus assay is higher in active TB patients compared to patients with LTBI and those who did not infect by TB. We found a greater level of specific IFN-γ obtained from TB2 in the DM-TB group compared to the DM-LTBI group and DM-only group. Our study showed that there were only a small number of patients in DM-LTBI group who gave CD8+ response, and it is consistent with the concept that latent TB represents some stages of the immune system and mycobacteria that have reached their balance. In this situation, CD8+ cells play an important role in controlling mycobacteria, establishing limitation of defended mycobacteria but resulting in tissue damage.[22,23] Increased expression of pro-inflammatory cytokine levels indicates high bacterial load in patients with DM and TB and as a consequence of delayed initial control on replicating MTB and increased tissue damage resulting from the weak response of cytokines

in patients with latent TB.[24,25]

Our study is the first study that establishes a prediction probability for active TB development from latent TB in patients with DM, and one of its factors is cathelicidin level. Until now, there is no consensus on the normal cathelicidin serum level; therefore, the results of our study that obtained a cutoff point of cathelicidin level in DM patients with latent TB are novel findings.

Study limitation

Our study utilized the QFT Plus assay, which is the newest generation of IGRA to detect latent TB, therefore providing better accuracy in diagnosing latent TB in patients with an assumed immunocompromised condition such as DM. Our study used case–control design to observe the factors affecting latent TB in DM; however, the method is still not adequate to study causality or prediction when it is compared to the prospective design method. The measurement of 25(OH)D_3 and 1,25$(OH)_2D_3$ Vitamin D levels in our study has used the method that has been regarded as the best method for measuring Vitamin D level, including measuring its active form of 1,25$(OH)_2D_3$. However, in this case, our study limitation is that we did not perform the measurement of 25$(OH)D_3$ and 1,25$(OH)_2D_3$ Vitamin D level simultaneously or at the same time. Moreover, we also did not perform any test for evaluating VDR and CYP27B1 to observe the whole status of Vitamin D and its metabolites as well as polymorphism factors that may affect Vitamin D status. Our study also did not measure nutrient adequacy and the amount of sun exposure in the patients.

Conclusion

Based on the screening of latent TB in DM patients, we found that 33.2% patients have been diagnosed with latent TB. There was a statistically significant difference in cathelicidin LL-37 levels between DM patients with latent TB, pulmonary TB, and without TB infection. There was no significant difference between 1,25$(OH)_2D_3$ and 25$(OH)D_3$ levels in DM patients with latent TB, active TB, and without TB infection. History of smoking, HbA1c, and cathelicidin LL-37 levels were factors that affected the risk of developing active TB, which progressed from latent TB in DM patients. We found that the probability for predicting the development of active TB from latent TB in patients with DM was 88.7% when there was a history of smoking, HbA1c level >9.5%, and cathelicidin level >30 ng/mL.

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Conflicts of interest

There are no conflicts of interest.

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