

Correlation of HbA1C and TNF- α Levels in Diabetic Patients with Pulmonary Tuberculosis after Intensive Phase of Tuberculosis Treatment

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ABSTRACT

Introduction: In 2013, there are 8.5 million people with diabetes mellitus (DM) in Indonesia, placing the country as the 7th highest number of DM cases. The poor controlled of DM could lead to several manifestations, including tuberculosis (TB) infections. In TB patients, Tumor Necrosis Factor- α (TNF- α) helps controlling the infection, but it may cause insulin resistance. Until date, there is no study investigating the correlation of these two laboratory parameters. We aimed to perform the correlation of HbA1C and TNF- α level in DM with TB after intensive phase of TB treatment.

Methods: The study was conducted from August to September 2019 in USU Hospital, Madani Medan Hospital, and Teladan Health Center. Patients diagnosed as DM type 2 with current insulin treatment were recruited. TB cases were determined by microscopic tests and X-ray. Blood specimens were drawn before and after intensive phase of treatment.

Results: We included 25 subjects in total, 19 (76%) were male. The laboratory data of subjects showed high level of HbA1C (9.40 ± 0.96 g%). Mean TNF- α of subjects was 503.87 ± 77.02 pg/mL. The data analysis showed significant decrease of TNF- α and HbA1C levels before and after intensive phase of antituberculosis treatment ($p = 0.000$; $p = 0.000$), positive correlation of TNF- α and HbA1C levels after intensive phase of antituberculosis treatment ($r = 0.791$; $r = 0.827$; $p = 0.000$)

Conclusion: There was significant decreased level of HbA1C before and after 2 months TB

treatment. HbA1C level did not have significant correlation to TNF- α level.

Keywords: diabetes, tuberculosis, HbA1C, TNF- α , cytokine

INTRODUCTION

Disease burden due to diabetes mellitus (DM) have increased and kept rising due to global rise of obesity prevalence and sedentary lifestyles.^[1] There are 415 million people with DM worldwide, as more than 85% cases are DM type 2 (DMT2). It is believed that the number increases every year and it is estimated 642 million people will be living with DM by 2040.^[2] In 2013, there are 8.5 million people with DM in Indonesia, making it as the 7th country with the highest number of adults with DM. In 2036, it is predicted, there will be 14.1 million adults with DM.^[1]

Diabetes mellitus is an independent risk factor for tuberculosis (TB) due to its deteriorating effect on immune system. Studies shows that DM increased risk of getting TB by 20 times.^[3] Nine million new cases of TB are reported annually, resulting in one third of world's population infected with *Mycobacterium tuberculosis*.^[4] In 2014, there were 9.6 million pulmonary TB worldwide. Indonesia is the second highest prevalence of pulmonary TB after India,^[5] with prevalence ranging from 12.8% to 42% around Indonesia.^[3] Pulmonary TB in DM

tend to be more severe than non-DM patients.^[3,6] Therefore, clinicians should have more attention to these cases.

HbA1C level was used to diagnose and monitor DM progress.^[7] HbA1C level is affected by number of factors and parameters, such as, tumor necrosis factor- α (TNF- α), a cytokine that is involved in systemic inflammation and mainly secreted by macrophages. It is also an essential component of innate defense mechanism against pathogenic challenge.^[8] In TB patients, TNF- α helps controlling the infection, but it may cause insulin resistance. On the other hand, TNF- α has found to have deteriorating effects in blood glucose control (fasting blood glucose, 2-hour post-prandial blood glucose and HbA1C levels).^[9] Intensive phase of antituberculosis treatment has high ability in eradicating *Mycobacterium tuberculosis*.^[9] It is hypothesized that after intensive phase, TNF- α levels will change, resulting in improved blood glucose control. So far, there is no study investigates on the changes of the TNF- α levels in DMT2 patients with pulmonary TB after anti-tuberculosis treatment.

Considering the evidences and data above, the aim of this study is to determine the correlation of TNF- α and HbA1C levels in DMT2 patients with pulmonary tuberculosis after intensive phase of anti-tuberculosis treatment. As TNF- α can help clinicians in predicting infection status and blood glucose control in DM patient with TB, we believe this study is still very much needed.

METHODS

The study was conducted from August 2019 to September 2019. Included subjects were more than 18 years old and diagnosed as DM type 2 with current insulin treatment. Subjects were also screened for pulmonary TB coinfection during visiting outpatient clinic in USU Hospital, Madani Medan Hospital, and Teladan Health Center. TB cases were determined by

microscopic tests and X-ray. Subjects were excluded whether they: 1) had other co-infections and antibiotics therapy recently, 2) were diagnosed as extrapulmonary TB, 3) were loss-to-follow up after 2 months of intervention, 4) had severe side effects and had to stop the treatment, 5) had severe comorbidity that would heavily affect drugs pharmacokinetics and pharmacodynamics, 6) were unwilling to continue their participation during the research process. This research was approved by Health and Research Ethics Commission. Blood specimens were taken before and after intensive phase of anti-tuberculosis treatment and examined in the Laboratory of RSUP Haji Adam Malik Medan. Data analysis was performed using Statistical Package for the Social Sciences (SPSS) 25 software.

RESULTS

We included total 25 subjects in our study. The baseline characteristics of subjects were shown in Table 1. Most of the included subjects initially did not achieve target blood glucose levels.

Table 1. Characteristics of Subjects

Variable	n = 25
Sex	
Male, n (%)	19 (76)
Age (year) ^a	56 (43-62)
Hemoglobin levels (g/dL) ^b	11,27 \pm 0,96
Leucocyte (10 ³ /mm ³) ^b	8,87 \pm 2,95
Thrombocyte (10 ³ /mm ³) ^b	341,72 \pm 112,21
FBG (g/dL) ^b	193,92 \pm 50,78
2h-PG (g/dL) ^a	256 (141-493)
HbA1C (g%) ^b	9,40 \pm 0,96
TNF- α (pg/mL) ^b	503,87 \pm 77,02
^a abnormal distribution, interpretation in median (min-max)	
^b normal distribution, mean \pm SD	
FBG: Fasting blood glucose; 2h-PG: 2 hour-postprandial glucose level.	

Correlation of TNF- α and HbA1C Levels

There was significant decrease of TNF- α and HbA1C levels before and after intensive phase of antituberculosis treatment ($p = 0,000$; $p = 0,000$) [Table 2]. Fasting blood glucose and 2-hour post prandial blood glucose were also significantly decrease after intensive phase treatment ($p = 0,000$).

Table 2. Comparison of Laboratory Parameter

Variable	Pre-Tuberculosis Intensive Treatment	Post Tuberculosis Intensive Treatment	p
FBG (g/dL) ^b	193,92 \pm 50,78	114,2 \pm 18,35	0,000 [*]
2h-PG (g/dL) ^a	256 (141-493)	188 (145-243)	0,000 [*]
HbA1C (g%) ^b	9,40 \pm 0,96	8,66 \pm 0,91	0,000 [*]
TNF- α (pg/mL) ^b	503,87 \pm 77,02	344,70 \pm 57,69	0,000 [*]

^a abnormal distribution, interpretation in median (min-max); Wilcoxon test;
^b normal distribution, mean \pm SD; t-paired test;
^{*}p < 0,05;
 FBG: Fasting blood glucose; 2h-PG: 2 hour-postprandial glucose level

There was positive correlation of TNF- α and HbA1C levels after intensive phase of antituberculosis treatment ($r = 0.791$; $r = 0.827$; $p = 0.000$) (Table 3). Negative correlation was found in fasting blood glucose and 2-hour post prandial blood glucose levels, but it was not significant ($r = -0.292$, $p = 0.157$; $r = -0.032$, $p = 0.530$). In our analysis, TNF- α level was negatively correlated with changes of blood glucose control after TB treatment (Table 4).

Table 3. Correlation test of FBG, 2h-PG, HbA1C and TNF- α Before and After Intensive Phase of Antituberculosis Treatment

Variable	r	p
FBG (g/dL) ^b	-0.292	0.157
2h-PG (g/dL) ^a	-0.032	0.530
HbA1C (g%) ^b	0.827	0.000 [*]
TNF- α (pg/mL) ^b	0.791	0.000 [*]

^a abnormal distribution; Spearman correlation test
^b normal distribution; Pearson correlation test
^{*}p < 0.05
 FBG: Fasting blood glucose; 2h-PG: 2 hour-postprandial glucose level

Table 4. Correlation of TNF- α level with the changes of FBG, 2-hours post prandial glucose, and HbA1C level

Variable	Changes in TNF- α	
	p	r
Changes in FBG (g/dL)	0,686	-0,085
Changes in 2h-PG (g/dL)	0,597	-0,111
Changes in HbA1C (g%)	0,351	-0,195

FBG: Fasting blood glucose; 2h-PG: 2 hour-postprandial glucose level

DISCUSSION

In our study, we found a significant decrease of HbA1C and blood glucose level after tuberculosis intensive treatment. Our finding was supported by Krishnappa et al.^[10] In their study, 65.4% of the subjects were found euglycemic after the treatment. DM and TB are two identities which could lead to vicious cycle and promote the progress of each other. High blood glucose state could cause abnormal immune function, impaired chemotaxis and

macrophage activation which would enable the colonization of TB.^[11] On the other hand, TB infection is known to cause stress which leads to higher cortisol level and plasma glucose level. The release of various cytokine during inflammatory process which may cause *concomitant pancreatitis*. As the hyperglycemic state occurred, the function of beta cell increases and causes amylin to deposit in pancreatic islet. In its severe stage, this condition could also lead to invasion of Mycobacteria to pancreas.^[10] By administering tuberculosis therapy, it will cause the decrease level of Mycobacteria. Thus, eliminating infection as the cause of stress.

We also found a significant decreased level of TNF- α after tuberculosis treatment. TNF- α was known to have two-sided mechanisms in TB infection. TNF- α acts to modulate immune response to Mycobacteria infection, stimulate granuloma formation, and inhibit the growth of Mycobacteria.^[12] TNF- α also could inhibit the insulin transduction leading to affect glucose metabolism and progression to diabetes mellitus.^[13] To our knowledge, the level of TNF- α decreased due to the subsided inflammatory response of infection. This finding was similar to some studies.^[14-16] Mvungi et al also found decreased level of others cytokine level, such as IFN- γ , IL-6, IL-10, dan IL-4 ($p < 0.0001$).^[15]

We also found TNF- α was negatively correlated with blood glucose control. However, this finding was not significant. In diabetes mellitus, Niazi et al found the level of TNF- α was decreased significantly compared to healthy subjects.^[17] The decreased of TNF- α could lead to impaired clearance of

Mycobacterium tuberculosis, macrophage function, chemotactic, and phagocytosis as well. These findings were supported by Montoya et al. They found phagocytosis of Mycobacteria was inversely correlated with plasma glucose level.^[18] The underlying mechanism was the impaired of CD86, CD80, and HLA DR expression which play vital role in presenting antigen to T-helper cells and cause the decreased level of IL-6, IL-1 β , IL-10 and IL-12.^[18]

There are some limitations of our study, such as, small sample size included. We also did not take into account some confounding factors, such as patient's diet, severity of TB and DM, and medications in our analysis. Despite the potential limitations, our study provided additional information on TNF- α and HbA1C level which would affect clinician in the settings to monitor the disease and evaluate the treatment progress.

CONCLUSION

There was significant decreased level of HbA1C before and after 2 months TB treatment. HbA1C level did not have significant correlation to TNF- α level.

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