

ORIGINAL ARTICLE

Glycemic Control Effect on Acid-Fast Bacteria Conversion in Diabetic Patients with Tuberculosis

Pengaruh Kontrol Glikemik dengan Konversi Sputum BTA pada Pasien Diabetes Melitus dengan Tuberkulosis

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ABSTRACT

Background

Diabetic people have a 2-3 times higher risk of tuberculosis than non-diabetic people. Immunocompromised conditions due to diabetes increase the risk of therapeutic failure and delayed sputum conversion, which may be caused by poor glycemic control. This study was conducted to determine the glycemic control effect on AFB conversion in diabetic patients with tuberculosis.

Methods

A cross-sectional study has been conducted on 100 diabetic patients with the new emergence of pulmonary tuberculosis. All patients were in intensive phase treatment of tuberculosis for two months at Bhayangkara R. Said Sukanto's Hospital. Data collected from medical records were random blood glucose level, percentage of random blood glucose decrement, HbA1C, and the microscopic AFB sputum smear. Fisher exact test analysis was conducted to determine the effect of random blood glucose level, percentage of blood glucose decrement and HbA1C to AFB smear results using SPSS V25.0 software for Windows with a significance level of 0.05.

Results

The analysis between glycemic control and AFB sputum smear conversion using random blood glucose, percentage of random blood glucose decrement and HbA1C showed a p-value of 0.000, indicating a significant relationship ($p < 0.05$), so it showed that glycemic control affects AFB sputum smear conversion.

Conclusions

A significant relationship exists between glycemic control and AFB-negative conversion in patients with DM and TB. RBG showed the best sensitivity and specificity as a glycemic control parameter compared to others.

Keywords: glycemic control; random blood glucose; HbA1C; RBG decrement; AFB negative conversion; tuberculosis; diabetes mellitus

ABSTRAK

Latar Belakang

Penderita diabetes melitus (DM) memiliki risiko 2-3 kali lebih tinggi menderita tuberkulosis (TB) dibandingkan dengan orang tanpa DM. Gangguan imunologi pada DM dapat meningkatkan risiko kegagalan terapi dan penundaan konversi sputum. Salah satu faktor yang dapat mempengaruhi konversi sputum adalah kontrol glikemik. Penelitian ini dilakukan untuk mengetahui hubungan kontrol glikemik dengan konversi sputum BTA pada pasien DM dengan TB.

Metode

Penelitian *observasional analitik* dengan desain studi potong lintang (*cross-sectional*) menggunakan rekam medis 100 orang pasien yang telah terdiagnosis DM dan TB kasus baru yang telah menjalani pengobatan TB fase intensif selama dua bulan di Rumah Sakit Bhayangkara R. Said Sukanto. Variabel yang dikumpulkan dan yang akan diteliti dari rekam medis adalah hasil tes darah Gula Darak Sewaktu (GDS), persentase penurunan GDS dan HbA_{1C} serta hasil sputum BTA mikroskopik. Analisis data menggunakan uji Fisher dan diolah dengan program SPSS V25.0 for windows dengan tingkat kemaknaan yang digunakan 0,005.

Hasil

Hasil analisis antara kontrol glikemik dengan konversi sputum BTA dengan menggunakan GDS, persentase penurunan GDS dan HbA_{1C} menghasilkan nilai $p = 0.000$ yang menunjukkan terdapat hubungan yang bermakna ($p < 0.05$) berdasarkan uji Fisher, sehingga dapat disimpulkan bahwa terdapat hubungan yang bermakna antara kontrol glikemik menggunakan GDS, persentase penurunan GDS, dan HbA_{1C} dengan konversi sputum BTA.

Kesimpulan

Terdapat hubungan bermakna antara kontrol glikemik dengan konversi sputum BTA pada pasien DM dengan TB. Berdasarkan sensitivitas dan spesifisitasnya, kadar GDS merupakan parameter yang lebih unggul dibandingkan 2 parameter lainnya.

Kata Kunci: kontrol glikemik, GDS, HbA_{1C}, persentase penurunan GDS, konversi sputum BTA, tuberkulosis, diabetes melitus

INTRODUCTION

Tuberculosis is a global health problem affecting almost 23% of the world's population, with 10 million new cases yearly. In developed countries, tuberculosis infection seems mostly found in certain groups, such as diabetic persons. Since obesity and diabetes mellitus become a worldwide problem, the increased risk of tuberculosis infection with worse clinical manifestations and treatment failure needs to be concerned.¹ A population-based cohort study by Lee et al. in Eastern China showed that diabetes increased the hazard of tuberculosis, especially in individuals with poor glycemic control and high blood lipid level.² The prevalence of pulmonary tuberculosis rises with the increased incidence of diabetes, with higher morbidity and mortality.³ In Indonesia, the prevalence rate of tuberculosis in 2010 was about 289 per 100,000 population, estimated at 450,000 new cases, and an incidence rate of 189 per 100,000 population. It made Indonesia the 5th country in the world in tuberculosis infection.^{4,5}

Pulmonary tuberculosis in adults is usually made based on clinical presentation and chest X-ray examination and confirmed by acid-fast bacilli found in microscopic examination.⁶ On the other hand, diabetes mellitus is a chronic high blood glucose level due to impaired insulin secretion,

known as type 1 diabetes, or hampered action of insulin or a combination of both, known as type 2 diabetes.⁷ This condition can affect the immune system, leading to susceptibility towards infections, including TB. A recent meta-analysis reported that the relative risk of TB in diabetic patients was 3.11 (95% CI 2.27–4.26) compared with individuals without DM in cohort studies.⁸ Another meta-analysis, including 17 studies involving more than 1 million participants, found that the pooled OR of prevalent TB was increased 2.05 fold in subjects with HbA_{1c}>7.0% compared to those with HbA_{1c}<7.0%.⁹

There are controversies about whether glycemic control affects negative sputum conversion, where some studies showed that there was no connection between them¹⁰, and many other studies showed the opposite.^(4,11–14) This study was conducted to determine the effect of glycemic control, which showed by random blood glucose level (RBG), HbA_{1c} and the percentage of blood sugar level decrement, to the negative sputum conversion in diabetic patients with pulmonary tuberculosis. Even though many studies have been performed, this study will try to determine which parameter of the three used showed the best sensitivity and specificity in affecting negative sputum smear conversion.

METHODS

This is an analytic observational study using a cross-sectional design conducted in Rumah Sakit Bhayangkara R. Said Sukanto – Kramat Jati – Jakarta from 12 September until 12 October 2018. Data were taken from the medical record. The population of the study were diabetic patients diagnosed with pulmonary tuberculosis as new cases from January 2017 to July 2018. The inclusion criteria were those above 35 years of age with newly found positive sputum smear from January 2017 to July 2018 that have been intensively treated for two months and evaluated for sputum smear, RBG, and HbA_{1c} by the end of the second month. The exclusion criteria were smokers, patients with HIV or extrapulmonary tuberculosis, and patients with multi-drug resistance (MDR-TB) or who dropped out of therapy before two months. Subjects of this study were taken using consecutive non-random sampling. The number of samples needed was calculated with the Infinite and Finite populations (the prevalence of TB in diabetic patients was 28.2%).¹⁵ Samples were added with a 15% dropout, so the total number of subjects needed for this study was 97. Data for this study were taken from the subjects' medical records, including demographic data (age and gender), confirmation of newly recorded positive sputum smear, and results of laboratory findings for RBG, HbA_{1c} and sputum conversion before and after intensive tuberculosis treatment for two months. Data collected was then analyzed univariately for characteristic distribution and bivariate for the relationships between glycemic controls (RBG, HbA_{1c}, blood glucose decrement) and negative sputum conversion, using Statistical Package for Social Sciences (SPSS) program for Windows version 25.0. The proposal for this study was approved by Komisi Etik Riset Fakultas Kedokteran Universitas Trisakti no 63/KER-FK/VIII/2018 on July 2018.

RESULTS

Characteristics of subjects

One hundred subjects were included in this study, which is dominated by a group of 56-65 years of age (4; most of the subjects are male (67%). Based on glycemic control, most subjects have a controlled RBG, less than 200 mg/dL (79%) and controlled HbA_{1c}, less than 7% (72%). The

percentage of RBG decrement from these subjects mostly was at a range of 31-50% (42%), followed by more than 50% (24%), while subjects with uncontrolled RBG decrement were 9%. Of these 100 subjects, 77% showed microscopic negative sputum smear of acid-fast bacilli conversion.

Table 1. Subjects characteristics

Variable	N	%
Age (years old)		
35-45	8	8.0
46-55	40	40.0
56-65	42	42.0
>65	10	10.0
Sex		
Male	67	67.0
Female	33	33.0
Serum glucose level by the end of therapy		
Controlled (<200 mg/dL)	79	79.0
Uncontrolled (\geq 200 mg/dL)	21	21.0
HbA_{1c} level by the end of therapy		
Controlled (\geq 7%)	72	72.0
Uncontrolled (<7%)	28	28.0
Percentage of serum sugar decrement		
Uncontrolled	9	9.0
\leq 10%	5	5.0
11-30%	20	20.0
31-50%	42	42.0
>50%	24	24.0
Microscopic sputum smear conversion by the end of therapy		
Positive	23	23.0
Negative	77	77.0

Relationship between glycemic control and negative sputum smear conversion

RBG and negative sputum smear conversion

Results showed that the subjects with controlled RBG had a higher percentage of negative sputum smear conversion. In contrast, subjects with uncontrolled RBG microscopic AFB sputum smear remained positive, and only one subject showed negative sputum smear conversion. Analysis using the Fisher test (p-value of 0.000) indicated that there is a significant relationship between RBG and AFB sputum smear conversion

HbA_{1c} and negative sputum smear conversion

The subjects with controlled HbA_{1c} had a higher percentage of negative sputum smear conversion. In contrast, in subjects with uncontrolled HbA_{1c}, microscopic AFB sputum smear in most subjects remains positive (20 from 28 subjects). The Fisher test analysis (p-value of 0.000) indicated a significant relationship between HbA_{1c} and AFB sputum smear conversion.

RBG decrement and negative sputum smear conversion

Groups of subjects with 31-50% decrement of RBG showed the highest percentage of negative sputum smear conversion (42%), followed by subjects with more than 50% RBG decrement (24%) compared to subjects with uncontrolled RBG decrement that showed only 9% AFB sputum smear

conversion. The Fisher test analysis (p-value of 0.000) indicated a significant relationship between RBG decrement and AFB sputum smear conversion.

Table 2. Relationship between glycemic control and negative sputum smear conversion

Glycemic control	Microscopic AFB negative smear conversion				Total		p value
	Positive		Negative		N	%	
	N	%	N	%			
Random blood glucose level (RBG)							0.000*
Controlled (<200 mg/dL)	3	3.0	76	76	79	79.0	
Uncontrolled (≥200 mg/dL)	20	20.0	1	1.0	21	21	
HbA1C							0.000*
Controlled (<7%)	3	3.0	69	69.0	72	72.0	
Uncontrolled (≥7%)	20	20.0	8	8.0	28	28.0	
RBG level decrement							0.000*
Uncontrolled	7	7.0	2	2.0	9	9.0	
≤ 10%	5	5.0	0	0	5	5.0	
11-30%	6	6.0	14	14.0	20	20.0	
31-50%	3	3.0	39	39.0	42	42.0	
>50%	2	2.0	22	22.0	24	24.0	

* Fisher exact test

DISCUSSION

Univariate analysis

Based on univariate analysis of data collected, it was found that TB in diabetic subjects is dominated mainly by the elderly group (> 45 years old). This finding was similar to the result from a study conducted by Kulsum et al. and Wijayanto et al. at RSUP Persahabatan. The average age of TB in diabetic patients was 53.71 and 58.6 years. It might be caused by glucose intolerance that increases with age. The aging process is one of the main factors of insulin sensitivity decrement, mitochondrial dysfunction, decrement of proliferative capacity and increase of apoptosis of pancreatic β cells. Lifestyle also contributes to insulin sensitivity, especially in older people with less physical activity and higher consumption of carbohydrates and fat.^{10,15}

The analysis also showed that most subjects are men. It is similar to reports from the Department of Gender and Women's Health World Health Organization which stated that tuberculosis incidence and prevalence were higher in men than women. This may be caused by risk factors and higher exposures that are more common in men, such as smoking, working environment, air pollution, industrial pollution etc.¹⁴ This finding differed from the results of the Wijayanto et al. study, which found that TB in diabetic was higher in women (59.2%) compared to men (40.8%). Unfortunately, there was no further explanation about it.¹⁵

This study also showed that most subjects had good glycemic control, as shown in RBG (79% compared to 21%), HbA1C (72% compared to 28%) and RBG decrement (42% with 31-50% and 24% with more than 50% decrement compared to 9% with uncontrolled decrement). This result was in line with microscopic AFB negative sputum smear conversion found in 77% of the subject compared to 23% who remained AFB positive. This showed that good glycemic control gives a better response to TB therapy.^{4,12,14-16}

Bivariate analysis

According to bivariate analyses, it was found that all three indicators showed a strong relationship between glycemic control and negative AFB sputum smear conversion, that is, using RBG, decrement of RBG and HbA_{1c}, with p-value = 0.000 (< 0.05). The table also showed that negative conversion in patients with controlled RBG and HbA_{1c} were higher than those who remained positive (76% to 3% and 69% to 3%, respectively). In the uncontrolled group, it was found that fewer subjects showed negative AFB sputum smear conversion (1% to 20% and 8% to 20%, respectively). It has been known that uncontrolled high blood sugar levels affect the interaction of monocyte and *M. tuberculosis* bacteria, decreasing the immune system. Poor glycemic control also reduces serum anti-TB drug concentration. It increases the risk of its toxicity, resulting in TB treatment failure, and the sputum AFB smear will remain positive.^{9,11,17-20} Another study also showed that poor glycemic control also affects the radiographic manifestation of pulmonary TB in diabetic patients.²¹

Based on RBG decrement, it has been found that patients with 31-50% RBG decrement had the highest percentage of negative AFB sputum smear conversion, followed by those with more than 50% decrement (39% and 22%, respectively). On the other hand, those with less RBG decrement showed unsuccessful conversion (7% in uncontrolled decrement, 5% in less than 10% decrement groups) p-value value of 0.000 using Fisher exact study conducted by Mahisale et al. pointed out that optimal glycemic control will give better success in therapy. It also decreased the risk of multi-drug resistance in TB treatment (MDR-TB). This same suggestion was also found in a study of TB control by Alisjahbana et al. in Indonesia that suggested that DM may implicate TB control in Indonesia.^{15,22} This result differed from a study by Ocegüera et al., which found no significant differences in smear and culture conversion between patients with TB and patients with TB+DM, including cases with inadequate glycemic control and those with MDR-TB.²³ The difference may be caused by the subjects of the study being largely different. In their study, patients with TB + DM were significantly older than TB patients without DM with significantly higher RBG levels. At the end of their discussion, they also mention that although deficient glycemic control does not correlate with culture conversion, diabetes harms TB treatment outcomes, with higher failure, relapse, and mortality rates.

This study was conducted using three different parameters of glycemic control (RBG, HbA_{1c} and RBG decrement). We tried to calculate the sensitivity and specificity of each parameter to find the best parameter, using the formula of sensitivity that is true positive compared to all sick subjects (true positive + false negative) and specificity that is true negative compared to all healthy subjects (true negative + false positive). The calculation found that RBG has the highest sensitivity, followed by RBG decrement and HbA_{1c} (98.7%, 97.4% and 89.6%, respectively). As for specificity, RBG and HbA_{1c} shared the same percentage, 86.9%, while RBG decrement was the lowest (30.4%). From that calculation, we assume that RBG can be chosen as the best parameter with the highest sensitivity and specificity.

The limitation of this study is that we only compare the effect of glycemic control to negative AFB sputum smear conversion without analyzing other factors that can interfere with the success of therapy, such as smoking, family support, or other medication consumed.

This study was conducted to find the relationship between glycemic control and the success of TB treatment in diabetic patients. From this result, we hope all subjects understand the

importance of compliance in lifestyle adjustment to reach better glycemic control, so the failure of TB treatment can be avoided.

CONCLUSION

Glycemic control was strongly associated with the success of TB treatment. Negative AFB sputum smear conversion was higher in controlled diabetic patients, with pulmonary higher negative conversion in the controlled group. RBG can be used as a glycemic control parameter as it has good sensitivity and specificity.

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AUTHORS CONTRIBUTION

As the principal researcher, DS prepares proposals, collects research data, and reviews and approves manuscripts. LMS reviews proposals, prepares manuscript drafts, and approves manuscripts

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CONFLICT OF INTEREST

There is no conflict of interest between the two authors in this study.

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