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## IMPACT OF UNCONTROLLED HbA1c ON THE OUTCOME OF TUBERCULOSIS TREATMENT IN TB PATIENTS WITH DIABETES

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### ABSTRACT

Pulmonary tuberculosis (TB) is an infection and communicable disease caused by *Mycobacterium tuberculosis*. One of the risks to develop active tuberculosis is diabetes mellitus (DM), with two or three times higher than TB patients without DM. Several studies have reported that DM was associated with poor clinical outcomes characterized by a delay of smear sputum conversion or culture conversion in TB patients with DM. However, very limited studies that analyze uncontrolled diabetes by HbA1c level with clinical outcome of TB treatment. This study aims to review the correlation between HbA1c levels and sputum or culture conversion in TB patients with DM. Pubmed, Web of Science, and Embase database were used to search and select the article. We included five studies that met the inclusion criteria. Smear conversion rate at two months was lower in TB patients with DM than those without DM. Uncontrolled HbA1c levels > 6.5%-7.0% were significantly associated with smear conversion of culture conversion for more than two months with a high risk of treatment failure. The positive level of smear sputum at 2-3 months or the end of the intensive phase becomes a strong predictor a failure treatment at the end of the advanced phase. It can be concluded that HbA1c levels delay the smear sputum or culture sputum for more than two months. This review highlights a need for more attention to control HbA1c levels in TB patients with DM to achieve a better outcome.

**Keywords:** Tuberculosis, Diabetes Mellitus, HbA1c, Smear Conversion, Culture Conversion

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### INTRODUCTION

Pulmonary tuberculosis (pulmonary TB) is an infectious disease caused by *Mycobacterium tuberculosis* and still an unresolved problem worldwide. About a third of the world's population is thought to have a latent infection of *Mycobacterium tuberculosis*, and 95% of them were found in developing countries. One of the risk factors for tuberculosis is diabetes mellitus (DM).<sup>1</sup> It was supposed that diabetic patients have a dysregulation of the immune system that leads to tuberculosis development. Diabetic patients have several times fold risk of suffering from TB than those without DM. Based on the world health organization(WHO),

Indonesia is estimated as the fifth highest country with diabetes in 2025.<sup>2</sup>

Several studies reported that diabetes mellitus has negative impacts on antituberculosis treatment. DM was significantly associated with culture sputum that was still positive after six months of treatment of antituberculosis. A meta-analysis study by Baker et al. showed different sputum culture conversion findings after 2-3 months of treatment with antituberculosis in TB patients with DM. The risk of treatment failure was 1.7 times higher than those without DM.<sup>3</sup> A high risk of infection, especially tuberculosis among type 2 diabetes mellitus (T2DM) patients, may

depend on HbA1c as a glycemic control parameter. Some studies including randomized trials and observational, have consistently shown that good glycemic control could reduce the risk of diabetic microvascular complications by 10%–25%.<sup>4,5</sup> However, the effect of HbA1c level on infections has not been examined in randomized trials.<sup>6,7</sup> Because of the data from some observational studies, it was difficult to interpret the data from inconsistent results. Furthermore, the HbA1c level usually was measured at once in patients with prevalent diabetes, making it difficult to understand the importance of acute hyperglycemia or hyperglycemia for a long time.<sup>8</sup>

Hemoglobin A1c (HbA1c) is glycated hemoglobin and is considered as a mean glucose level over the past 90 days.<sup>9</sup> The measurement level of HbA1c has a strong relationship with the prevalence of type 2 diabetes mellitus (T2DM) in numerous studies. In T2DM, patients with a high level of HbA1c with more than 53mmol/ml are associated with an increased risk of active pulmonary TB.<sup>10</sup> An association between DM and time to sputum conversion in TB patients has been observed by Alisjahbana et al., who stated that the failure of sputum conversion at the end of the second month of treatment TB in TB patients with DM was higher than those without DM. Still, his study did not evaluate some factors that affect sputum conversion.<sup>11</sup> Moreover, diabetes mellitus has been reported by several studies as the main factor that inhibits sputum conversion at the end of the second month of TB treatment. The proportion of sputum culture conversion at two months after the intensive phase of TB treatment in TB with T2DM was 17.1% and without DM was 18.3%, and it seems to be similar. However, at the end of the advanced phase (four months), the positive culture was higher in T2DM patients (22.2%) compared to patients without T2DM (9.6%).<sup>11</sup> A study by Wijayanto et al. stated that the level of HbA1c more than 8% was associated with TB in T2DM patients.<sup>12</sup>

A high level of HbA1c would increase the risk failure of sputum smear conversion 2.3 more significant in TB patients with diabetes. Although many studies have reported that diabetes was one of the risk factors that impaired the outcome of antituberculosis drugs, few studies analyze the association between HbA1c and sputum smear or sputum culture conversion in TB patients with diabetes. However, most of the published studies were observational studies. These findings remain unclear because of the differences in sample type of TB patients, methods, time to diagnose DM during TB treatment, etc. In this review, we discussed whether a high level of HbA1c impaired the tuberculosis treatment of TB patients with DM in sputum smear or sputum culture conversion

## METHODS

This review aims to determine whether uncontrolled HbA1c impaired the TB treatment in TB-DM patients compared to TB without DM in sputum smear or sputum culture conversion.

We collected the articles from Pubmed, Web of Science, and Embase database published in 2015-2020. We used published articles, both written in English and Indonesia. The keywords to search the articles were: tuberculosis AND "diabetes mellitus" AND (HbA1C or "glycemic control" AND "sputum smear conversion" or "sputum culture conversion" The selected articles, including titles and abstracts, will be read and screened that matches the purpose of this study.

We used the articles for both retrospective and prospective studies. The inclusion criteria in this review were: (1) studies both experimental design (randomized controlled trial) and observational (cohort, cross-sectional, and case-control) that analyze or discuss HbA1c, (2) patients were diagnosed pulmonary TB with diabetes as well as HbA1c data and sputum results were available, (3) all patients in both groups were measured sputum smear or sputum culture conversion at 2-3 months or sixth

months. We excluded the articles if: (1) animal experiments study, (2) reviews, letters, brief communication and case report study, (3) pulmonary TB patients complicated with autoimmune or immunodeficiency diseases such as systemic lupus, rheumatoid arthritis which need long-term use of steroids, (4)

multidrug-resistant (MDR-TB) and extra-pulmonary TB.

## RESULTS

Five studies met the inclusion criteria from several databases, as shown in table 1.

**Table 1.** Article Characteristics.

Author and Year	Study Design	Number of Subjects	Findings
Ratnawati et al., 2018 <sup>13</sup>	A prospective cohort study of new cases of pulmonary TB	123	HbA1C level more than 47.5 mmol/ml was a significant relationship with sputum conversion for more than two months, RR 6.3 (1.9-39.6) (p<0.05)
Kulsum et al., 2017 <sup>14</sup>	A prospective cohort study of new cases of TB	84	After two months of intensive phase failures in TB-DM patients, the proportion of sputum conversion was 43.04% vs. 22.75% (p<0.05). HbA1C level is one of the risk factors for conversion failure (p=0.014)
Ocegüera et al., 2015 <sup>15</sup>	A retrospective study of TB cases during five years	88	Time to sputum conversion in patients TB+DM with HbA1C more than and less than 6.5% was 68.9 days vs. 110.0 days, respectively (p>0.05). Time to culture conversion in MDR-TB patients with DM was 93.5 days vs. 75.9 days in MDR-TB patients without DM (p>0.05)
Yoon et al., 2017 <sup>16</sup>	A prospective cohort study of pulmonary TB	661	TB patients with DM who had uncontrolled diabetes (HbA1c > 7%) were significantly associated with the positive culture after two months of treatment, treatment failure, and death (p<0.05). Patients with controlled DM has a favorable outcome treatment similar to the non-DM group.
Chiang et al., 2015 <sup>17</sup>	A prospective cohort study of pulmonary TB	1.473	Diabetic patients with HbA1c > 9% were significantly more likely to be smear-positive than those without diabetes.

## DISCUSSION

### *The Correlation Between DM and Infection (TB)*

Pulmonary TB and DM are chronic and related diseases. Pulmonary TB will not recover sufficiently in uncontrolled diabetes. Pulmonary TB patients with DM have different characteristics, so they often

undiagnosed, and therapy is challenging due to the interaction between TB drugs and oral antidiabetics. Factors associated with pulmonary TB in T2DM were close contact with other TB patients, the length of suffering from DM, and HbA1c levels. Wijayanto et al. reported that patients who have diabetes for a long time have a significant association with

TB infection in DM patients (OR 23.13; CI 95% 4.6-11), but it did not examine the relationships between the length of suffering from DM sputum conversion.<sup>12</sup> Measurement of HbA1c levels was more accurate to predict the prognosis of TB in TB-DM patients compared to blood glucose level. HbA1c level described blood glucose levels during the past 2-3 months and was not influenced by oral antidiabetic medication or food taken soon before the examination.

Several studies have reported that high-level HbA1c was associated with increased TB infection risk, but many of them did not analyze the association with sputum conversion. A systematic review of the observational study by Jeon et al. reported that low blood sugar control or uncontrolled HbA1c significantly increases the risk of infection TB with a hazard ratio of 1.39 per unit of increase in HbA1c levels (CI 95% 1.18-1.63).<sup>18</sup> A study by Bartelink et al. stated that there was no significant difference in average levels of HbA1c in T2DM patients with and without infection. In contrast, patients who had an infection during the follow-up period showed a higher level of HbA1c compared to patients without infection. Several studies have measured at once HbA1c levels on specifically selected infections.<sup>19</sup> A poor glycemic control characterized by a high level of HbA1c was associated with systemic infections,<sup>20,21</sup> pneumonia requiring hospitalization,<sup>22</sup> tuberculosis (TB),<sup>23</sup> urinary tract infections,<sup>24</sup> and woman reproductive infection.<sup>25</sup> A study by Critchley et al. stated that poor glycemic control in diabetic patients was significantly associated with severe infections such as bone and joint infection (46%), tuberculosis (24%), and sepsis (21%).<sup>26</sup>

### ***Association Uncontrolled HbA1c With Therapeutic Outcome of Antituberculosis Treatment***

Several studies have reported uncontrolled diabetes, characterized by HbA1c level > 7% among T2DM with TB. A study by Wahiduddin et al. stated that the HbA1c level in DM patients with pulmonary TB was higher (11.2%) than those without pulmonary TB (9.3%). This study was also reported that less than T2DM with TB achieving HbA1c level <7%.<sup>27</sup> Several studies reported a high proportion of uncontrolled diabetes with HbA1c levels of more than 7% in T2DM with TB. Boyilla N et al. reported that in T2DM with pulmonary TB, the proportion of HbA1c > 9% was 58.33%, while HbA1c <7% was 15.28%.<sup>28</sup> Ahmed M et al. found most of the T2DM patients with pulmonary TB, 58.6% had uncontrolled HbA1c levels (> 6.5%).<sup>29</sup> It indicated that the glycemic control in T2DM with TB was poor.

Based on table 1, all of the studies were observational with a cohort design. Studies reported that uncontrolled diabetes with HbA1c > 7% was significantly associated with positive smear sputum or positive culture at a second month or the end of the intensive phase. One hypothesis showed that T2DM with TB impaired the antituberculosis treatment outcome. This condition is due to the immune dysregulation function. Several studies evaluating immune function in T2DM patients reported a dysregulation immunity, both innate and adaptive immunity. The dysregulation immunity was characterized by decreased interleukin 1 (IL-1) and IL-6 secretion by neutrophil cells and monocytes. It can decrease mobilization, chemotaxis, phagocytosis of phagocytic cells. It was also decreased T cell response and impaired humoral immunity.<sup>30,31</sup>

Natural killer (NK) cell functions and their relationship with glycemic control level have not been widely studied.<sup>32</sup> NK cells are very important against viral and bacterial infections as well as control cancer growth. Meanwhile, T2DM patients with poor glycemic control have a higher risk of viral or bacterial infections and cancer. Previous studies reported a reduction activity of NK cells in T2DM,<sup>33,34</sup> but studies relating glycemic control and NK cells research activity were very rare. A study by Berrou et al. reported that a decreased NK cell activity in T2DM patients was negatively correlated with HbA1c levels.<sup>33</sup> Several mechanisms are thought to explain these findings: hyperglycemia against the expression of glucose transporter (GLUT1, GLUT3, and GLUT4).<sup>35</sup>

Glucose is an important energy source for metabolism and cell activity, including immune cells such as leukocytes and NK cells. Impaired transporter expression of glucose will cause NK cells to lack energy and unable to activate their function. Besides, hyperglycemia in T2DM patients causes stress on the endoplasmic reticulum and leads to low expression of NK cell activation receptors such as NKG2D<sup>33</sup>. Furthermore, poor glycemic control in DM patients can disrupt NK cell activity, explaining DM patients' increased susceptibility against viral or bacterial infections and cancer. However, Ristanti et al. reported that the glycemic control did not significantly correlate with NK cell activity in T2DM.<sup>36</sup>

A study by Kulsum et al. reported that the median level of HbA1c in the non-conversion group was significantly 10% higher than HbA1c levels in the conversion group (8.5%). A high level of HbA1c was also associated with increased failure of sputum conversion after correcting in albumin and acid-fast bacilli (AFB) positive level before

antituberculosis treatment ( $p = 0.018$ , aOR 1.298, CI 95% 1.047-1.610).<sup>14</sup> The study by Jiyani et al. was also reported that 50% of patients who had sputum smear positivity before therapy (3+) were TB-DM patients with HbA1c levels  $> 8\%$ . Still, this study did not analyze the relationship between HbA1c levels and sputum conversion.<sup>37</sup>

In experimental animal models with chronic hyperglycemic, inflammatory cells and mediators are similar. It is even higher than that in euglycemic animals. However, there is a decrease in the cellular immune response. This was also characterized by inadequate binding and ingesting of the peripheral blood monocytes (PBM) with *M. tuberculosis* in T2DM patients.<sup>38</sup> A proposed mechanism for the disability of macrophages to respond to *M. tuberculosis* in diabetic patients may be due to the reduction in nitric oxide production and  $H_2O_2$  in the macrophages,<sup>39</sup> processes in which PARP1 is actively involved.<sup>40,41</sup> Therefore, diabetic patients, especially with HbA1c levels above 8%, were associated with a longer time to smear or culture conversion and a higher incidence of treatment failure

### ***Interaction of Diabetes With Antituberculosis Drugs***

It has been proposed that there were significant interactions between antituberculosis drugs and oral antidiabetic. And it was also worsening in the clinical outcome of TB patients with DM. Several studies have examined the effect of diabetes mellitus on the PK-PD of antituberculosis drugs. The results were contradictory or inconsistent. Several studies on TB patients with DM showed that the concentration of antituberculosis drugs was lower.<sup>42-44</sup> While other studies reported no differences in antituberculosis concentration.<sup>45,46</sup>

Antituberculosis medications concentration on TB-DM patient's, especially rifampicin, was lower than in TB without DM. It was because of the alteration of drug absorption, distribution, and elimination (metabolism and excretion) in TB patients with DM. A study by Nijland et al. stated that the serum concentration of rifampicin in TB patients with DM was 53% lower than in TB patients without DM. A low concentration of antituberculosis drugs was predicted to cause poor clinical outcomes, and the risk of treatment failure was nine folds higher than that of high concentration.<sup>42</sup>

A study by Kusibawati et al. reported interaction between rifampicin and sulphonylurea, glipizid. It was found that rifampicin can stimulate the formation of cytochrome P-450 isoenzyme CYP2C9 to metabolize glipizid. Rifampicin accelerates the elimination of glipizid and lowers the glipizid concentration in blood circulation. Rifampicin is also proven to induce potent hepatic microsomal enzymes. Rifampicin also plays a role with another drug metabolism in the mixed-function oxidase (MFO) system. This system acts in a first-phase oxidase reaction in drug metabolism.<sup>47</sup>

An optimal therapy strategy for TB patients with DM has not been established. There is no best scientific evidence that supports the differences in regimen, especially antituberculosis drugs, between TB patients with and without DM. For TB patients with DM, the therapy and duration of antituberculosis medications are similar to TB patients without DM. In the intensive phase, four regimens of antituberculosis drugs (rifampicin, isoniazid, ethambutol, and pyrazinamide) are given daily for two months. In the advanced phase, rifampicin and isoniazid are administered daily or intermittently for four months, when blood sugar is well controlled. However, when

blood sugar is poorly controlled, it will be extended to seven until nine months.

A systematic review reported that intermittent treatment in the advanced phase has a higher risk of treatment failure, relapse, and drug resistance than daily dose therapy. In 2017, WHO has no longer recommended intermittent treatment in the advanced phase. Interestingly, a study by Siane et al. stated that there were no differences between smear conversion and success rate in the advanced phase in TB patients with DM between daily and intermittent treatment.<sup>48</sup> However, this study has some limitations. This study was a retrospective study from the medical record of TB-DM patients. The number of patients was relatively small, so it can't directly be applied to the general population.

A recent study by Alfarisi et al. reported that DM influenced pyrazinamide's pharmacokinetics. It also increases maximum concentration (C<sub>max</sub>) above the therapeutic concentration. A high level of C<sub>max</sub> of pyrazinamide was significantly associated with treatment failure, relapse, and death. The therapeutic concentration against *Mycobacterium tuberculosis* of rifampicin, isoniazid, and pyrazinamide is 8 mcg/ml, 3 mcg/ml, and 35 mcg/ml, respectively. Among the antituberculosis drugs, only pyrazinamide has a significantly lower TB concentration with DM than those without DM. In addition, an increase in HbA<sub>1c</sub> levels was followed by a decrease in pyrazinamide concentration. TB patients with DM, the concentration of rifampicin and isoniazid, were positively associated with time to culture conversion, but not with pyrazinamide concentration.<sup>49</sup> In TB patients with DM, the rifampicin concentration was significantly reduced compared to TB patients without DM.

Interestingly, data from several studies were contradictory. Some studies reported a slower absorption and reduced rifampicin

concentration.<sup>43</sup> While others showed no significant effect of DM on the pharmacokinetics profile of rifampicin.<sup>50</sup> It was because of the differences in demographic patients, the severity of DM, the dose of antituberculosis drugs, and study design. In the continuous phase, rifampicin with a dose of 450 mg-600 mg was administered to TB patients thrice weekly or well known as intermittent dose and has been associated with worsened clinical outcome. Thus, a higher and daily dose of rifampicin is needed to achieve a targeted clinical outcome.

A low concentration of isoniazid in TB patients with DM may be related to DM-induced intestinal motility changes. Due to isoniazid metabolization through N-acetyltransferase 2 (NAT2), the rapid acetylators population reduces the plasma level of isoniazid<sup>51</sup>. Whether patients with DM should be administered a higher dose of antituberculosis was not clearly stated. An adequate dose of isoniazid (which reduces tuberculosis bacterial quickly) and rifampicin (which is the key sterilizing drugs) as the main anti-TB drugs in six months of therapy, including intensive and continuous phase, was needed to achieve sputum or culture conversion.

Insulin, oral hypoglycemic agent, and the combination between insulin and hypoglycemic agent improved the HbA1c level in T2DM with TB was observed by Wahiduddin et al. In T2DM with TB patients who uses insulin, oral hypoglycemic agent, and combination, HbA1c level was 10.29%, 12.23%, and 11.12% respectively. It was much higher than those without TB.<sup>27</sup> However, this study did not report the type and dose of insulin and oral hypoglycemic agent that alter the HbA1c level, so it must carefully interpret in clinical settings.

Conversely, a hypoglycemic event resulting from the interaction between

isoniazid and glimepiride was reported by Boglou et al. Primarily, glimepiride is metabolized in the liver via the cytochrome P450 isoenzyme CYP2C9 to its active metabolite and then metabolized to its dehydrogenated inactive metabolite. The inhibition process of cytochrome leads to the accumulation of parent drug glimepiride, resulting in hypoglycemia. Isoniazid, one of the antituberculosis drugs, is a strong inhibitor of CYP2C9 and other cytochrome P450 isoenzymes such as CYP2C19 and CYP2E1. Therefore, co-administration with glimepiride could increase its concentration in blood circulation.<sup>52</sup> Thus, administration of isoniazid in DM patients, especially with concurrent acute illness who receive glimepiride may increase the risk of hypoglycemic events

## CONCLUSION

From this review, it can be concluded that uncontrolled diabetes, which is characterized by a high level of HbA1c > 6.5-7.0%, was significantly associated with delay of sputum smear conversion or culture conversion more than two months in TB patients with DM. Clinicians and pharmacists should collaborate to increase attention to HbA1c level or glucose level in TB patients with DM to achieve a better clinical outcome and reduce severe prognosis.

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