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ORIGINAL ARTICLE

The relationship between HbA1c control levels and antituberculosis treatment effects: a meta-analysis

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Abstract

Background: Multiple studies of tuberculosis (TB) treatment have indicated that patients with diabetes mellitus (DM) may experience poor outcomes. We performed a meta-analysis to summarize evidence for the relationship between HbA1c control levels and anti-TB treatment effects in patients afflicted with both TB and DM.

Methods: Both English and Chinese databases were searched. Chinese databases included CNKI, WanFang, SinoMed, and VIP. PubMed, Ovid MEDLINE, Embase, Cochrane Library, and Web of Science were searched for English articles. We included studies that were restricted to the relationship between HbA1c levels and anti-TB treatment effects (sputum conversion rate [SCR] and TB focus absorption) in diabetic patients receiving treatment for TB. We used RevMan 5.3 software to analyze the data.

Results: We included 12 studies, of which five reported SCR at 2 months, seven reported the conversion at 3 months, and seven reported TB focus absorption. According to the five studies which reported 2 months-SCR, patients with diabetes and TB had an odds ratio (OR) of 2.14 (95% CI: 0.84-5.43) for the 2 months-SCR between controlled (HbA1c <7.0) and uncontrolled diabetes (HbA1c ≥7.0). However, additional seven studies reporting 3 months-SCR showed that controlled diabetics had higher SCR than uncontrolled (OR 3.39, 95% CI: 2.12-5.43). Moreover, seven of the 12 studies demonstrated that there were differences in TB focus absorption between controlled and uncontrolled diabetes (OR 2.69, 95% CI: 1.91-3.79).

Conclusion: HbA1c control levels influence the SCR at 3 months and the TB focus absorption at the end of the anti-TB intensive treatment phase. This study highlights a need for increased attention to HbA1c or glucose control in patients afflicted with both TB and DM.

Keywords: Diabetes mellitus; Hemoglobin A; Meta-analysis sputum; Tuberculosis

1. INTRODUCTION

Recently, the global burden of diabetes mellitus (DM) has been rising, and tuberculosis (TB) remains a leading cause of morbidity and mortality throughout the world. Epidemiological studies have elucidated an association between DM and the development of TB disease. According to a recent systematic review among cohort studies, people with DM had approximately three times the risk of developing TB as those without DM.[1] The uncontrolled glucose may lead to an increased incidence of various infectious diseases, including TB; moreover, it may also decrease the effectiveness of anti-TB treatments for DM-TB patients. Clearly, it is important for DM-TB patients to monitor their glucose levels. The TB clinical manifestations in DM-TB patients have a close relationship with glucose control levels; however, glucose levels fluctuate wildly and are easily influenced by various factors. TB manifestations may reflect transient glucose levels, but they are ineffective in evaluating diabetes control. The HbA1c is the product of glucose binding to hemoglobin in red blood cells, which is a slow, continuous, and irreversible combining process. It is a better marker of blood glucose control, as it measures blood glucose over a period of 2 to 3 months and is not subject to the rapid swings that can occur with random and fasting blood glucose measurements.[2] HbA1c testing is beneficial for diagnosis, treatment, and prognosis of DM. Some studies have suggested that controlled diabetics seem to have lower positive smear rates and higher culture conversion rates after 2 months of anti-TB therapy.[3] On the contrary, some studies have reported that there are no differences between treatment time and culture conversion in controlled and uncontrolled diabetes.[4–8] A unified view has yet to be reached regarding whether the HbA1c control levels are the most influential factors of anti-TB treatment effects. This meta-analysis was performed to determine whether control status of diabetes influences anti-TB treatment outcomes by monitoring HbA1c.

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2. METHODS

2.1. Study selection

2.1.1. Inclusion criteria

Studies were included if they met the following criteria: (1) randomized controlled, case-controlled, or cohort studies that

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discuss HbA1c control status, sputum smear positive rates, and TB focus absorption; (2) All patients were diagnosed with both DM[4] and TB, at the same time, HbA1c data, sputum results, and the TB focus absorption condition were available for the study; (3) main outcome measures: controlled and uncontrolled DM were defined as HbA1c <7.0% and HbA1c ≥7.0%, respectively. All patients in both groups received sputum conversion results at 2 and 3 months of anti-TB treatment; secondary outcome measures: the TB focus absorption at the end of the anti-TB intensive treatment phase; (4) TB therapy schedule included the standard TB therapy regime.[10]

Note that HbA1c provides a measure of blood glucose over a period of 2 to 3 months, and the anti-TB intensive treatments include a 2- and 3-month regime. In general, the sputum will convert after 2 months of anti-TB treatment. Based on these data, we decided to collect sputum conversion results at 2 and 3 months.

2.1.2. Exclusion criteria

We excluded the following: (1) animal experiments, (2) systematic reviews, lectures, or comments; (3) studies repeated and published many times; (4) incomplete medical records, such as studies that did not report at least one of the TB outcomes listed earlier; patients complicated with congenital or secondary immunodeficiency diseases, such as HIV infection; diseases which need long-term use of glucocorticoids, such as autoimmune diseases, organ transplantation, etc; drug-resistant TB and extrapulmonary TB; and (5) pregnant and lactating women. Excluded reports were less than 10 cases.

2.1.3. Languages

Both English and Chinese databases were searched.

2.1.4. Compliance with ethical standards funding

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee, the 1964 Declaration of Helsinki and its later amendments, or comparable ethical standards.

2.1.5. Informed consent

Informed consent was obtained from all individual participants included in the study.

2.2. Publication search

We screened the articles by adopting the combined search methods of computer and manual retrieval. All studies performed were searched from the earliest documents until April 1, 2016, in electronic databases, including Ovid MEDLINE, Embase, Cochrane Library, PubMed, Web of Science, CNKI, SinoMed, WanFang, and VIP. Concurrently, citations in these studies were also searched. We reviewed the retrieved studies and researched the references.

2.3. Search strategy

The following search terms were applied: tuberculosis, Mycobacterium tuberculosis, tuberculosis infection, tuberculosis disease and diabet*, HbA1c, and glycated hemoglobin. We restricted our search to publications in English and Chinese. All titles and abstracts were read to select the appropriate studies addressing the impact of HbA1c on TB outcomes. Unpublished sources of data were not included, as the current large number of DM-TB studies make the presence of publication bias improbable. All search keywords were used in conjunction with the free words.

2.4. Data extraction and study quality assessment

Two reviewers independently collected data from the selected studies using a data extraction form designed before starting the study, and the methodological qualities of the studies were assessed independently. Differences were resolved by consensus and discussion.

The quality of the randomized controlled trials (RCTs) was assessed using the risk of bias assessment tools of the Cochrane systematic review. Cohort and case–control studies were evaluated in accordance with the Newcastle–Ottawa Scale (NOS). The Cochrane systematic review risk of bias assessment tools includes six aspects: random method, allocation concealment, blinding method, incomplete outcome data, selective reporting, and other bias. NOS includes four entries of the research object: comparability between the groups is one entry, and outcome measures have three entries. The total score is nine points, and scores less than six are rated as B-class, while the others are rated as A-class.[11]

2.5. Statistical analysis

The RevMan 5.3 software of the Cochrane Collaboration was used to conduct the meta-analysis. The odds ratio (OR) was used as the statistic of the count data (sputum conversion rate [SCR] or TB focus absorption), and the effect size was performed using a 95% CI. Z (U) test was used to test the OR values, and $p < 0.05$ was considered statistically significant. Inconsistency (statistical heterogeneity) among studies was assessed by the conventional Chi-square-based Q test for heterogeneity, When $p > 0.05$ or $I^2 < 50\%$ in the Q test, it indicated that good homogeneity existed, and a fixed-effect model (Mantel–Haenszel method) was used; otherwise, it showed there was some heterogeneity, and a random-effect model (DerSimonian–Laird method) was used. Sensitivity and subgroup analysis were used to evaluate potential sources of homogeneity. Sensitivity analysis was conducted by excluding studies successively to check the stability of the results, and publication bias was assessed by funnel plots.

3. RESULTS

3.1. Literature search and quality assessment

According to the predetermined retrieval scheme, a total of 1106 studies were screened; we excluded duplicate studies, consulted the abstracts, and finally 12 studies (Fig. 1) were included. The general information is shown in Table 1, and all of the studies

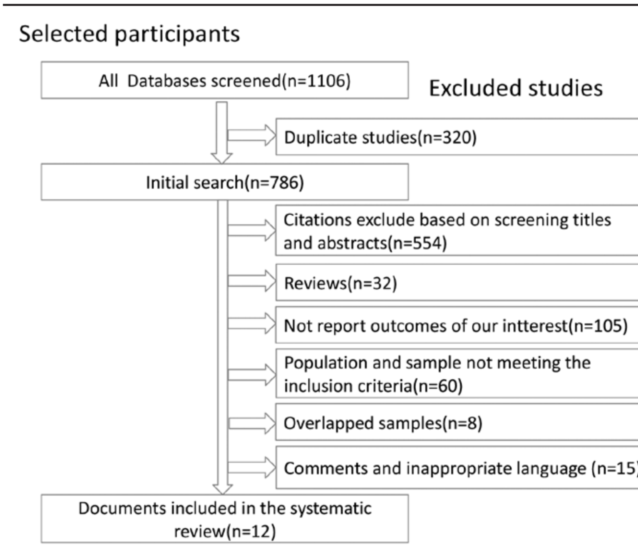

Fig. 1. The literature screening processes and outcomes.

Table 1

General information of included studies

	Controlled Diabetes (HbA1C <7.0)				Uncontrolled Diabetes (HbA1C ≥7.0)					
Study	**Samples (n)**	**Age (y)**	**TB Therapy Schedule**	**DM Therapy Schedule**	**Samples (n)**	**Age (y)**	**TB Therapy Schedule**	**DM Therapy Schedule**	**Follow-up Time**	**Quality Assessment**
Li and Han[14]	42	64.6 ± 9.5	3HRWZ/6HRE	Early insulin therapy	42	64.9 ± 9.4	3HRWZ/6HRE	Oral taking gliclazide, and insulin therapy would be performed when oral medicine was useless	At 2 months	Moderate risk
Ge[19]	30	Unclear	3HRZE/6HR	Subcutaneous injection of Gan Shulin 30R 30 min before morning and evening meal	30	Unclear	3HRZE/6HR	Glimepiride 2 mg QD, the maximum dose is not more than 8 mg, metformin TID 0.25 g, the maximum dose is not more than 1.5 g.	At 3 months	Moderate risk
Wang and Xu[16]	26	47.4 ± 9.0	Unclear	Intensive insulin therapy: use Nuo Herui before meals and Novolin N before bedtime, when glucose is up to standard, injecting Nuo Herui 30R twice daily	26	48.5 ± 8.7	Unclear	Subcutaneous injection Novolin 30R twice daily	At 3 months	Moderate risk
Zhang[17]	40	56.21 ± 7.38	3HRZE/9HRE, and continuous subcutaneous injection of BCG polysaccharide nucleic acid for 3 months	Unclear	40	57.15 ± 7.52	3HRZE/9HRE	Unclear	At 3 months	Moderate risk
Huang et al[18]	23	Unclear	3HRZE/6HR	Subcutaneous injection of Novolin 30R 30 min before morning and evening meal	12	Unclear	3HRZE/6HR	Subcutaneous injection of Nuo Helin 30R 30 min before morning and evening meal	At 3 months	Moderate risk
Song[12]	36	49.56 ± 10.56	Unclear	Routine treatment and health education, and dietary intervention	36	42.70 ± 13.34	Unclear	Routine treatment and health education	At 2 months	High risk
Zhen et al[21]	33	50.47 ± 16.63	Unclear	Regular instant hypoglycemic, health guidance, outpatient individual health guidance and telephone follow-up, the use of Orem self-care therapy in nursing care	31	51.45 ± 15.32	Unclear	Regular instant hypoglycemic, health guidance	At 3 months	Moderate risk
Wang et al[22]	38	51 ± 4.3	3HRZE/6HR	Giving oral antidiabetic drug, insulin therapy if necessary; individualized diet for 28 days	38	51 ± 4. 3	3HRZE/6HR	Giving oral antidiabetic drug, insulin therapy if necessary	At 3 months	Moderate risk
Li et al[20]	55	52.8±15 .3	Unclear	Conventional hypoglycemic therapy, physician health guidance, follow-up nursing	55	52.8 ± 15.3	Unclear	Conventional hypoglycemic therapy, physician health guidance	At 3 months	Moderate risk
Chiang et al[13]	82	Unclear	Unclear	Unclear	428	Unclear	Unclear	Unclear	At 2 months	A
Park et al[8]	96	Unclear	Unclear	Unclear	28	Unclear	Unclear	Unclear	At 2 months	A
Jiang[15]	94	65.0±11.2	2HRZE/10HR	Unclear	164	65.0±11.2	2HRZE/10HR	Unclear	At 2 months	B

BCG = bacille calmette-guerin; DM = diabetes mellitus; TB = tuberculosis QD = once a day; TID = three times a day.

were conducted in Asia, which included nine RCTs (Table 2), two cohort studies, and one case–control study (Table 3). Eight of the nine RCTs were assessed as having a moderate bias risk, and one study had a high risk of bias. Two studies of the non-RCTs (NRCT) were assessed as A-grade, while another study was B-grade.

3.2. Results of the meta-analysis

The overall effect magnitude of this study is reflected in the ORs, and the weight of each independent research is shown in Figures 2 and 3. The SCR after 2 months of anti-TB therapy: five studies were included,[5–9] in which 348 were uncontrolled diabetes cases (HbA1c ≥7.0), 698 were controlled (HbA1C <7.0), and the treatment regime was 3HRZE/6HR. According to the tests for heterogeneity ($p < 0.05$), we intended to choose the random-effects model. The random-effects OR of the SCR between controlled and uncontrolled diabetes was 2.14 (95% CI: 0.84-5.43), the 95% CI contained the case of OR equaling 1, and $Z = 1.6$, $p = 0.11 > 0.05$; therefore, there was no statistically significant difference between these two groups. This indicated that after 2 months of anti-TB therapy, we could not believe that the SCRs of the well-controlled group were higher than that of the uncontrolled group (77.64% vs 73.63%) (Fig. 2). When analyzing the characteristics of the literature, we successively included the studies and conducted cumulative analyses by referring to the quality assessment. As a result, the OR point estimates and 95% CI were unstable and waved violently; however, there were two of the five studies that showed the existence of a statistically significant difference between these two groups.[14,16] According to the sensitivity analysis, except for the small sample size and the ambiguous description of the treatment regime, there was no correlation between the basic characteristics of the selected studies and the SCRs. We subsequently extracted the two articles successively, and the pooled results did not change. Next, we excluded these two studies, and the pooled OR was 1.30 (95% CI: 0.44-3.87), which was consistent with the previous results and indicated that the results were reliable. In addition, one article[13] in the five studies showed that the 2 months SCR of the uncontrolled group was less than that of the controlled group, but there was no statistical difference (OR was 0.57, 95% CI: 0.31-1.03). Sensitivity analysis was carried out, and the results of another four studies were statistically significant (pooled OR was 3.17, 95% CI: 2.01-4.99). Moreover, the four studies were homogeneous, and the results were not consistent with the meta-analysis. As for the study,[13] except for the large sample size disparity (82 cases were in the controlled group, 428 were in the uncontrolled group), some patients had no sputum results during follow-up, and there was no correlation between the basic characteristics of the selected articles and the SCRs. In addition, the number of uncontrolled group participants in this study was more than half of the whole uncontrolled group number (428/698), which was obviously higher than that of other studies. Thus, the difference between the sample size and the incomplete data may be the source of heterogeneity. The SCR after 3 months of anti-TB therapy: seven articles conform to the requirements,[10–16] among which, 205 were controlled and 201 were uncontrolled groups. According to the heterogeneity test ($p = 0.99$), the fixed-effect model was selected for meta-analysis. The SCRs of the controlled group were higher than that of the uncontrolled group (82.93% vs 58.71%), as the fixed pooled OR was 3.39 (95% CI: 2.12-5.43); that is to say the 3 months SCRs between these two groups were statistically significant ($p < 0.05$). Regarding the seven studies, the SCRs of the controlled groups were all higher than that of the uncontrolled groups, and four of these seven articles had no statistical difference.[16,18,19,22] Sensitivity analysis was performed, and the study was successively excluded; however, the results remained the same and proved that the analysis results were reliable (Fig. 3). The TB focus absorption at the end of anti-TB intensive treatment (2-3 months) was: there were seven studies comparing the absorption of TB focus between the controlled and uncontrolled groups,[12,14–19] with 275 controlled and 360 uncontrolled, and the results were not statistically different ($p = 0.99$), so the fixed-effect model was used. The results were statistically significant as the fixed pooled OR was 2.69 (95% CI: 1.91-3.79) (Fig. 4), which showed that the absorption of the TB focus in the HbA1c

Table 2

The methodological quality assessment of the RCT

Risk of Bias	High Risk	Moderate Risk	Moderate Risk	Moderate Risk	Moderate Risk	Moderate Risk	Moderate Risk	Moderate Risk	Moderate Risk
Other bias	Existing	Unclear	No	Unclear	No	no	No	no	Unclear
Selective reporting	No	No	No	No	No	No	No	No	No
Incomplete outcome data	Complete	Complete	Complete	Complete	Complete	Complete	complete	Complete	complete
Blinding method	Right	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Allocation concealment	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Random method	Right	Right	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Right
Study	Song[12]	Li and Han[14]	Li et al[20]	Zhen et al[21]	Huang et al[18]	Wang et al[22]	Zhang[17]	Ge[19]	Wang and Xu[16]

RCT = randomized controlled trial.

Table 3

The methodological quality assessment of the NRCT

Study	Study Design	Selection				Comparability	Exposure/Outcome			Total Score	Quality Grade
		①	②	③	④	⑤	⑥	⑦	⑧		
Park et al[8]	Case–control study	1	1	1	1	1	1	1	0	7	A
Chiang et al[13]	Cohort study	1	1	1	1	1	1	1	1	8	A
Jiang[15]	Cohort study	1	1	1	0	0	0	1	1	5	B

A study can be awarded a maximum of one star for each numbered item within the selection and exposure/outcome categories. A maximum of two stars can be given for comparability. ①, case definition adequate?/Representativeness of the exposed cohort; ②, representativeness of the cases/selection of the nonexposed cohort; ③, selection of controls/ascertainment of exposure; ④, definition of controls/demonstration that outcome of interest was not present at the start of the study; ⑤, comparability of cases and controls on the basis of the design or analysis; ⑥, ascertainment of exposure/assessment of outcome; ⑦, same method of ascertainment for cases and controls/Was follow-up long enough for outcomes to occur?; ⑧, nonresponse rate/adequacy of follow-up of cohorts.

NRCT = nonrandomized controlled trial.

Study or Subgroup	HbA1c<7% Events	HbA1c<7% Total	HbA1c≥7% Events	HbA1c≥7% Total	Weight	Odds Ratio M-H, Random, 95% CI
Chen Yuan Chiang2014	64	82	369	428	23.2%	0.57 [0.31, 1.03]
Lei Song2014	8	34	3	36	16.0%	3.38 [0.82, 14.04]
Ping Li2014	37	42	24	42	18.7%	5.55 [1.82, 16.94]
S.W.Park2012	83	96	22	28	19.1%	1.74 [0.59, 5.10]
Xiuhui Jiang2014	77	94	96	164	23.0%	3.21 [1.74, 5.91]
Total (95% CI)		**348**		**698**	**100.0%**	**2.14 [0.84, 5.43]**
Total events	269		514			

Heterogeneity: Tau² = 0.89; Chi² = 22.73, df = 4 (p = 0.0001); I² = 82%

Test for overall effect: Z = 1.60 (p = 0.11)

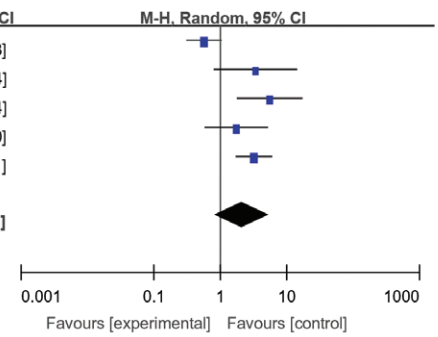

Fig. 2. The meta-analysis of the SCR between the controlled group and uncontrolled group after 2 months of anti-TB treatment. SCR, sputum conversion rate; TB, tuberculosis.

Study or Subgroup	HbA1c<7% Events	HbA1c<7% Total	HbA1c≥7% Events	HbA1c≥7% Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Chuanmei Wang2014	32	38	26	38	21.1%	2.46 [0.81, 7.46]
Guoqin Zhen2011	24	33	18	43	21.9%	3.70 [1.39, 9.84]
Huihua Li2013	35	45	23	43	26.9%	3.04 [1.21, 7.66]
Huizhong Huang2007	20	23	8	12	7.1%	3.33 [0.60, 18.37]
Peng Zhang2015	21	25	15	26	12.1%	3.85 [1.03, 14.45]
Xiaohua Wang2009	19	21	15	21	7.4%	3.80 [0.67, 21.60]
Zhenkun Ge2014	19	20	13	18	3.5%	7.31 [0.76, 70.03]
Total (95% CI)		**205**		**201**	**100.0%**	**3.39 [2.12, 5.43]**
Total events	170		118			

Heterogeneity: Chi² = 0.90, df = 6 (p = 0.99); I² = 0%

Test for overall effect: Z = 5.08 (p < 0.00001)

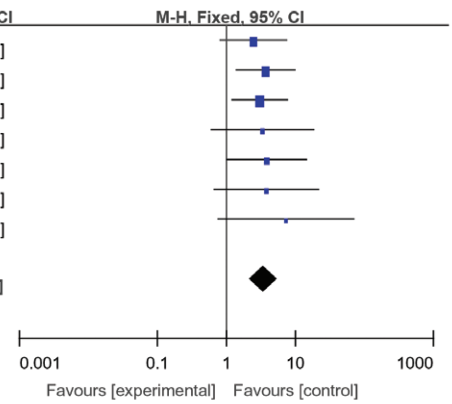

Fig. 3. The meta-analysis of the SCR between the controlled group and uncontrolled group after 3 months of anti-TB treatment. SCR, sputum conversion rate; TB, tuberculosis.

Study or Subgroup	HbA1c<7.0% Events	HbA1c<7.0% Total	HbA1c≥7.0% Events	HbA1c≥7.0% Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Ping Li2014	38	42	28	42	6.6%	4.75 [1.41, 15.99]
Zhenkun Ge2014	25	30	16	30	6.6%	4.38 [1.32, 14.50]
Peng Zhang2015	19	27	11	26	8.2%	3.24 [1.04, 10.07]
Xiaohua Wang2009	17	25	13	25	10.3%	1.96 [0.62, 6.19]
Huizhong Huang2007	15	23	17	37	11.2%	2.21 [0.75, 6.46]
Lei Song2014	26	34	21	36	11.9%	2.32 [0.83, 6.52]
Xiuhui Jiang2014	61	94	71	164	45.1%	2.42 [1.43, 4.09]
Total (95% CI)		**275**		**360**	**100.0%**	**2.69 [1.91, 3.79]**
Total events	201		177			

Heterogeneity: Chi² = 2.23, df = 6 (p = 0.90); I² = 0%

Test for overall effect: Z = 5.63 (p < 0.00001)

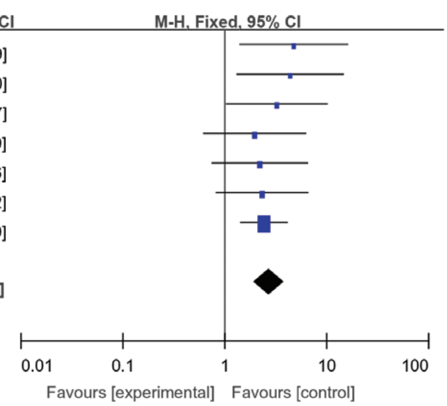

Fig. 4. The meta-analysis of the TB focus absorption at the end of anti-TB intensive treatment phase. TB, tuberculosis.

controlled group was better than the uncontrolled group. In addition, there were three of the seven studies comparing the 2 months anti-TB treatment:[12,14,15] 170 were controlled, and 242 were uncontrolled. Studies were not heterogeneous (p = 0.59), so the fixed-effect model was used, and the pooled OR was 2.64 (95% CI: 1.71-4.08). TB focus absorption between the two groups had a statistically significant difference (Fig. 5). Another four studies compared the results of the 3 months of anti-TB therapy:[16–19] 105 were controlled, 118 were uncontrolled, and a fixed-effect model was used, as the results among the studies had no statistical heterogeneity (p = 0.77), and the fixed pooled OR was 2.76 (95% CI: 1.57-4.86) (Fig. 6). The sensitivity analysis of the abovementioned results was carried out, and the results showed no change, which proved that the results were reliable.

Study or Subgroup	HbA1c<7.0% Events	HbA1c<7.0% Total	HbA1c ≥7.0% Events	HbA1c ≥7.0% Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Ping Li2014	38	42	28	42	10.4%	4.75 [1.41, 15.99]
Lei Song2014	26	34	21	36	18.7%	2.32 [0.83, 6.52]
Xiuhui Jiang2014	61	94	71	164	70.9%	2.42 [1.43, 4.09]
Total (95% CI)		**170**		**242**	**100.0%**	**2.64 [1.71, 4.08]**
Total events	125		120			

Heterogeneity: Chi² = 1.06, df = 2 (p = 0.59); I² = 0%

Test for overall effect: Z = 4.39 (p < 0.0001)

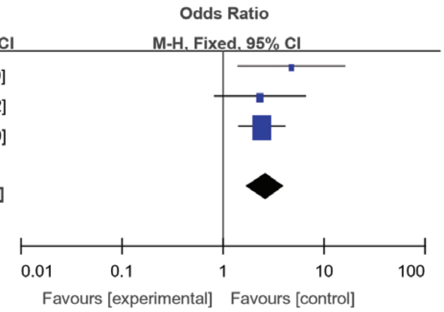

Fig. 5. The meta-analysis of the TB focus absorption after 2 months of anti-TB treatment. TB, tuberculosis.

Study or Subgroup	HbA1c<7.0% Events	HbA1c<7.0% Total	HbA1c≥7.0% Events	HbA1c≥7.0% Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Zhenkun Ge2014	25	30	16	30	18.2%	4.38 [1.32, 14.50]
Peng Zhang2015	19	27	11	26	22.6%	3.24 [1.04, 10.07]
Xiaohua Wang2009	17	25	13	25	28.3%	1.96 [0.62, 6.19]
Huizhong Huang2007	15	23	17	37	30.9%	2.21 [0.75, 6.46]
Total (95% CI)		**105**		**118**	**100.0%**	**2.76 [1.57, 4.86]**
Total events	76		57			

Heterogeneity: Chi² = 1.15, df = 3 (p = 0.77); I² = 0%

Test for overall effect: Z = 3.53 (p = 0.0004)

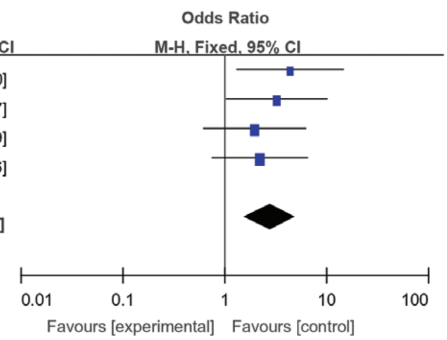

Fig. 6. The meta-analysis of the tuberculosis focus absorption after 3 months of anti-TB treatment. TB, tuberculosis.

The assessment of publication bias: We did not find evidence for publication bias by funnel plot for the SCR after 3 months of anti-TB treatments (Fig. 7).

4. DISCUSSION

DM and TB are chronic wasting diseases, and these two conditions can influence and promote each other. Relevant studies at home and abroad have found that the impact of diabetes on TB patients may be related to the following factors: (1) high blood glucose or deficiency of insulin secretion has provided a good environment for the survival of *Mycobacterium tuberculosis*; therefore, it is favorable to the colonization of the TB bacilli but unfavorable to the control of TB. (2) Abnormal immune function, impaired monocyte chemotaxis, damaged alveolar macrophage activation, decreased interferon gamma levels, and the change of type I cells live hormone expression can decrease the patients' ability to resist and remove *M. tuberculosis*, and as a result, it spreads in the body, which is not conducive to the control of TB.[23,24] (3) The interaction of rifampicin and hypoglycemic drugs reduced the absorption of rifampicin in patients with DM, which can influence the treatment effects of TB. There is evidence that rifampicin effects depend on the peak concentration of drug exposure time, which was lower in TB patients with DM than that of TB patients without DM. This directly affects the effectiveness of TB treatments and may lead to the production of acquired resistance.[25] (4) The high incidence of drug resistance in patients with DM complicated with TB makes it difficult to use the short-course chemotherapy for controlling the disease. It is known from the factors earlier that immune system disorders and respiratory system immunity decline may occur in patients when DM and TB are combined, which leads to a vicious cycle, since the therapeutic drugs for these two diseases are mutually negatively influenced. As one of the testing indexes of diabetes, the correlation between HbA1c and the severity of TB indirectly reflects the influence of diabetes on the treatment of TB. This study shows that in the first 2 months of treatment for diabetes and TB, the SCR of TB and the severity of TB show no obvious correlation, yet as the treatment continues, the control level of HbA1c exerts a direct influence upon the prognosis of TB; moreover, in cases of more than 2 months of anti-TB therapy, the focal absorption of those patients whose level of HbA1c is well controlled within a low level performs better than those whose level of HbA1c is poorly controlled; hence, maintaining the level of HbA1c at a low level is beneficial for therapeutic effects and outcomes. It can thus be seen that, as for the treatment of diabetes complicated with pulmonary TB, the control over diabetes, especially the level of HbA1c, is helpful for the improvement of patients' metabolism, thus adjusting

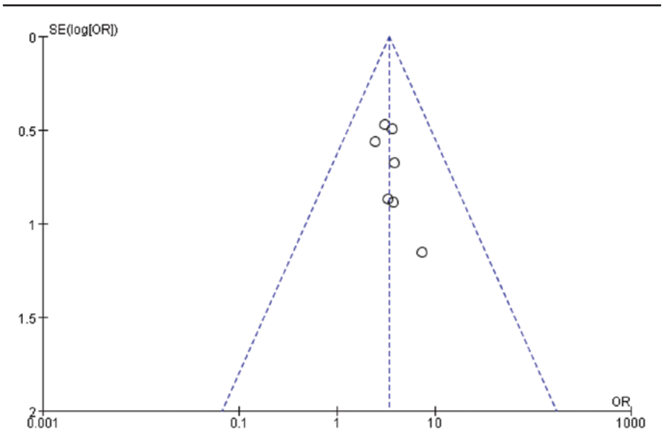

Fig. 7. The funnel plots of publication bias after 3 months of anti-TB treatment. TB, tuberculosis.

the functions of immune system and enhancing the immunity of patients. The time of anti-TB therapy should be appropriately extended, which is positively significant for its treatment. In short, it is crucial for diabetes patients to control their blood glucose level, since it is directly related to the emergence, development, treatment, and prognosis of TB.[2] Meanwhile, as the testing index of the control over diabetes, HbA1c directs the therapeutic schedule's making of diabetes and TB. During the anti-TB therapy, HbA1c is monitored regularly (1-3 months) to evaluate the control level of diabetes for timely adjustment of the blood glucose reduction schedule.

This study had some limitations. First, it included a small sample size, and most were derived from domestic research, making the study quality uneven. Second, the study of random methods and distribution of hidden and blind methods were not clear. Moreover, due to the long treatment period for TB, tests may be affected by more confounding factors, and patient compliance was also an important factor in response to the results. A survey[26] on TB medication compliance showed that compliance rates in 1 year were only 54%, as 46% of the patients failed to adhere to the standard treatment. More importantly, these 12 studies were not describing compliance rates. Furthermore, when making research plans, this study intended to include articles from different countries and regions, but eventually 10 of the included 12 studies were Chinese. The two English studies were conducted in Taiwan and South Korea, and such regional differences may affect the authenticity of the research. In a word, the abovementioned factors restrict the popularization and application of this research.

In conclusion, recent evidence suggests that the treatment principle should adhere to treating the two diseases at the same time. Not only should we provide regular anti-TB treatment, but we should also pay attention to the control of blood glucose in patients with DM via HbA1c: monitoring blood glucose or glycosylated hemoglobin values to make the diabetic blood glucose and HbA1c control stable over a long term. At the end, the two diseases have been effectively treated and controlled. However, due to the limitations of the methodology in the research, the reliability of the meta-analysis evaluation results is decreased. We look forward to higher quality study to further verify the effect of HbA1c levels on the treatment of pulmonary TB.

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