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ORIGINAL RESEARCH

Variations in Quinolinic Acid Levels in Tuberculosis Patients with Diabetes Comorbidity: A Pilot Prospective Cohort Study

Min Yang[1–3,*], Wenfei Wang[3,*], Peize Zhang[4], Guizhen Liu[5], Hailin Lu[6], Mingjie He[5], Guofang Deng[2,3], Xiaoyou Chen[1,7]

[1]Department of Pharmacology, Beijing Tuberculosis and Thoracic Tumor Research Institute, Beijing Chest Hospital, Capital Medical University, Beijing, People's Republic of China; [2]Second Department of Pulmonary Medicine and Tuberculosis, the Third People's Hospital of Shenzhen, Southern University of Science and Technology, Shenzhen, Guangdong, People's Republic of China; [3]National Clinical Research Center for Infectious Disease, the Third People's Hospital of Shenzhen, Southern University of Science and Technology, Shenzhen, Guangdong, People's Republic of China; [4]Fourth Department of Pulmonary Medicine and Tuberculosis, the Third People's Hospital of Shenzhen, Southern University of Science and Technology, Shenzhen, Guangdong, People's Republic of China; [5]The First Affiliated Hospital of Gannan Medical University, Ganzhou, Jiangxi, People's Republic of China; [6]Gannan Medical University, Ganzhou, Jiangxi, People's Republic of China; [7]Infectious Diseases Department, Beijing Ditan Hospital, Capital Medical University, Beijing, People's Republic of China

*These authors contributed equally to this work

Correspondence: Xiaoyou Chen; Guofang Deng, Email chenxy1998@hotmail.com; jxxk1035@yeah.net

Objective: We aimed to investigate dysregulated metabolic pathways and identify diagnostic and therapeutic targets in patients with tuberculosis-diabetes (TB-DM).

Methods: In our prospective cohort study, plasma samples were collected from healthy individuals, diabetic (DM) patients, untreated TB-only (TB-0)/TB-DM patients (TB-DM-0), and cured TB (TB-6)/TB-DM patients (TB-DM-6) to measure the levels of amino acids, fatty acids, and other metabolites in plasma using high-throughput targeted quantification methods.

Results: Significantly different biological processes and biomarkers were identified in DM, TB-DM-0, and TB-DM-6 patients. Moreover, quinolinic acid (QA) showed excellent predictive accuracy for distinguishing between DM patients and TB-DM-0 patients, with an AUC of 1 (95% CI 1–1). When differentiating between TB-DM-0 patients and TB-DM-6 patients, the AUC was 0.9297 (95% CI 0.8460–1). Compared to those in DM patients, the QA levels were significantly elevated in TB-DM-0 patients and decreased significantly after antituberculosis treatment. We simultaneously compared healthy controls and untreated tuberculosis patients and detected an increase in the level of QA in the plasma of tuberculosis patients, which decreased following treatment.

Conclusion: These findings improve the current understanding of tuberculosis treatment in patients with diabetes. QA may serve as an ideal diagnostic biomarker for TB-DM patients and contribute to the development of more effective treatments.

Keywords: pulmonary tuberculosis, diabetes, metabolomics, quinolinic acid, biomarker

Introduction

TB is the second leading cause of death from a single infectious agent after coronavirus disease, and more than 10 million people continue to contract TB every year, making it a significant global public health issue.[1,2] Currently, there are approximately 463 million diabetes patients globally, and this number is projected to increase to 700 million by 2045.[3] In addition to increased susceptibility to active tuberculosis, diabetes worsens the severity of tuberculosis.[4] TB-DM patients are more likely to experience delayed sputum culture conversion, treatment failure, and higher rates of relapse, with relapse rates twice those of tuberculosis patients without diabetes.[5,6] Therefore, the dual burden of TB-DM represents a major global public health concern. Timely assessment of novel diagnostic and treatment strategies for TB-DM patients remains a global priority.[7]

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Tuberculosis bacillus culture or acid-fast bacilli smear microscopy, along with chest imaging, are currently the standard methods used to monitor the response to treatment.[8] Imaging techniques, such as X-ray and computed tomography (CT) scans, may not yield notable changes in the initial stages of treatment. Furthermore, the sputum acid-fast bacilli smear microscopy technique has a high false-negative rate of up to 50%.[9] The tuberculosis bacillus culture technique is time-consuming and has a low sensitivity of approximately 30%, rendering rapid assessment challenging.[10,11] Thus, there is a pressing need for more rapid, accurate methods to assess the diagnostic and therapeutic targets of tuberculosis, especially in diabetic patients.

Metabolomics has been shown to be an effective method for exploring and identifying new diagnostic and prognostic biomarkers.[12] Numerous studies have demonstrated that serum untargeted metabolomics can distinguish between active pulmonary tuberculosis and latent tuberculosis infection as well as the sustained decrease in specific metabolites in patients after antituberculosis treatment. Metabolomic analysis may lead to the identification of potential biomarkers for diagnostic and therapeutic purposes.[13] Diabetes is a chronic metabolic disorder characterized by alterations in carbohydrate, lipid, and protein metabolism.[14] Immune-metabolic dysregulation in diabetic patients is closely associated with susceptibility to tuberculosis.[15] The linking the severity of TB in T2DM patients (type 2 diabetes) to elevated systemic levels of glycerol has also been reported.[16] However, there is limited research on the changes in metabolites following tuberculosis activity and after antituberculosis treatment in diabetic patients.

QA is a neuroinflammatory neurotoxin, it plays a role in the development of neurodegenerative processes.[17] QA has been linked to several brain disorders, including depression, Alzheimer's disease (AD), and schizophrenia.[18,19] For example, in individuals with depression, compared with healthy controls, peripheral QA concentrations are reportedly greater, and treatment for depression decreases QA concentrations.[20,21] In this study, we analysed metabolomic data from the plasma of healthy individuals, diabetic patients and tuberculosis patients with or without diabetes before and after anti-tuberculosis treatment. We identified metabolic changes associated with TB-DM treatment. Specifically, we found that the biomarker QA performed well in distinguishing DM patients from TB-DM patients, showed significant changes before and after TB-DM treatment. QA levels were significantly elevated in TB patients and decreased significantly after anti-tuberculosis treatment. These studies suggest that QA is a potential diagnostic biomarker and therapeutic target for TB-DM patients.

Method

Study Design and Participants

We have categorized our experimental groups into the following: Diabetic patients without tuberculosis (DM group), Diabetic patients with tuberculosis (DM-TB group), Healthy donors (HD group) for comparison, Tuberculosis patients without diabetes (TB-only group) for validation of tuberculosis-specific changes. Our aim is to compare the changes in plasma metabolites between DM patients and TB-DM patients in hopes of identifying diagnostic biomarkers. The inclusion of the HD and TB-only groups is to validate that these changes in biomarkers are indeed due to *M.tuberculosis* infection.

The DM group and TB-DM group were diagnosed with T2DM according to the WHO diagnostic criteria.[22] DM groups were 18–70 years who exhibited negative chest radiological signs and negative interferon-gamma (IFN-γ) release assay (IGRA) results. The inclusion criteria for patients in the TB-DM group were as follows: 1) aged 18–70 years; 2) diagnosed by Xpert and/or culture, with suggestive clinical and radiological findings; 3) had not started anti-TB treatment or had started it less than 2 weeks prior to the start of the study; and 4) were drug sensitive.

HDs were simultaneously recruited and underwent a physical examination with the following criteria: 1) aged 18–70 years old; 2) no respiratory symptoms such as cough, sputum, shortness of breath, dyspnoea, or chest pain; 3) no pulmonary lesions by chest X-ray or computed tomography.

TB-only patients were prospectively and consecutively recruited based on the following criteria: 1) aged 18–70 years old; 2) diagnosed by Xpert and/or culture, with suggestive clinical and radiological findings; 3) anti-TB treatment not initiated or started less than 2 weeks.

The exclusion criteria of the two groups included: 1) HIV infection; 2) rheumatologic autoimmune diseases; 3) tumours; 4) impaired liver or kidney function; 5) extrapulmonary tuberculosis; 6) history of previous tuberculosis; and 7) critical condition. The flow of participant enrolment is shown in Figure 1.

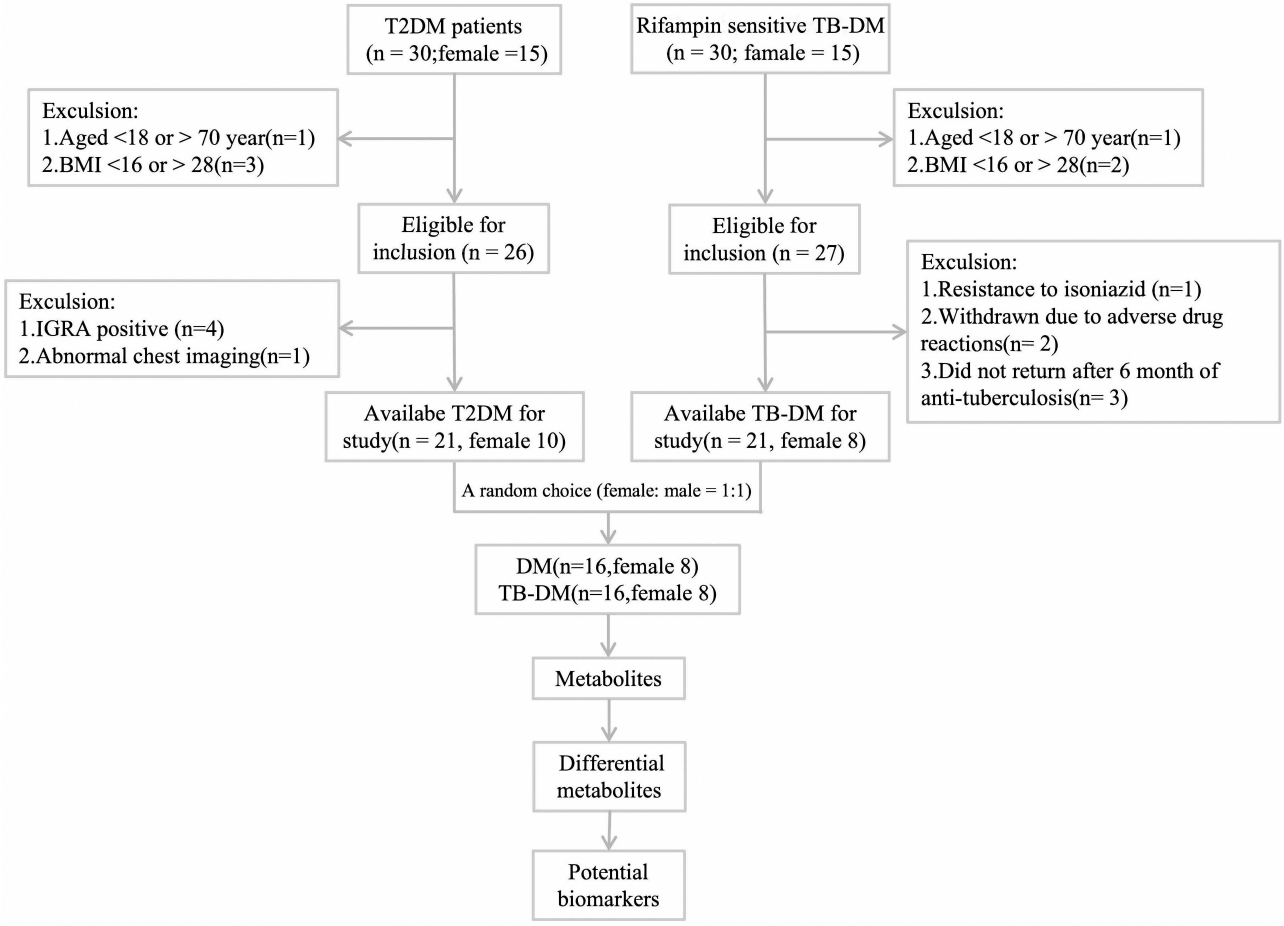

Figure 1 Flowchart of participant enrolment.

A total of 64 participants participated in this study (Table 1), among whom 16 had active pulmonary TB with diabetes (mean age 49.7 years; males, n = 8 [50%]), 16 had diabetes (mean age 43.9 years; males, n = 8 [50%]), 16 had TB-only (mean age 53.9 years; males, n = 8 [50%]), and 16 were healthy individuals (mean age 36.8 years, [range 34–49] years; males, n = 8 [50%]). All the TB patients completed their anti-tuberculosis treatment at the 6th month. Six months after completing the treatment, none of the patients exhibited symptoms such as coughing or sputum production, and both sputum acid-fast bacilli smears and tuberculosis cultures were negative.

Blood Sample Collection

Blood samples were collected in the morning from each group using anticoagulant tubes containing EDTA. Within two hours of collection, the samples were centrifuged at a force of 3000 × g for 10 minutes. The resulting plasma was then sectioned into cryovials and immediately frozen at a temperature of −80°C for storage.

High-Throughput Targeted Quantification of Metabolites

The sample extracts were analysed using a Waters UPLC I-Class Plus (Waters, USA) instrument equipped with a QTRAP 6500 Plus (SCIEX, USA) at the Department of Mass Spectrometry, BGI-Shenzhen. The protocol and chromatography conditions provided by the manufacturer were followed. The column used was a BEH C18 (2.1 mm × 10 cm, 1.7 μm, Waters). The mobile phase was water containing 0.1% formic acid (Solvent A) and acetonitrile containing 30% isopropanol (Solvent B). Elution was performed using the following gradient: 0–1.00 min, 5% B; 1.00–5.00 min, 5% B; 5.00–9.00 min, 70% B; 9.00–11.00 min, 50% B; 11.00–13.50 min, 22% B; and 13.5–14.00 min, 95% B. The flow speed above was 0.400 mL/min, which was also the flow speed for 14.00–16.00 min, 100% B. The flow speed was 0.600 mL/min for 16.00–18.00 min, 5% B. The column

Table 1 Study Population Characteristics

Characteristic	DM	TB-DM	Health	TB-only
Age, years (Mean±SD)	43.9±14.3	49.7±12.0**	36.8±9.6	53.9±10.0##
Sex, female	16, 8	16, 8	16, 8	16, 8
Body mass index, kg/m2 (Mean±SD)	22.1±2.3	23.7±2.5	20.8±1.6	21.4±2.0
Smear positive	–	7 (43.7%)	–	6 (37.5%)
Xpert MTB-RIF Positive	–	13 (81.2%)	–	14 (87.5%)
Mycobacterial culture positive	–	14 (87.5%)	–	15 (93.8%)
Cavitation	–	9 (56%)	–	2 (12.5%)
Treatment outcome, cure	–	16 (100%)	–	16 (100%)
Alcohol use				
Current or former	3	4	6	5
Never	13	12	10	11
Tobacco use				
Current or former	6	5	5	7
Never	10	11	11	9

Notes: The differences among DM and TB-DM groups were compared using unpaired *t* test, ** $p \leq 0.01$. The differences among Healthy and TB-only groups were compared using unpaired *t* test, ## $p \leq 0.01$.

temperature was 40°C. The mass spectrometry conditions were as follows. A QTRAP 6500 Plus with an ESI Turbo ion spray interface was used. The ion source parameters were as follows: ion source temperature, 400°C; ion spray voltage, 4500 V (positive mode) and −4500 V (negative mode); and ion source gas 1 (GS1), ion source gas 2 (GS2) and curtain gas, which were set to 60, 60, and 35 psi, respectively. The multiple reaction monitoring (MRM) Method was used in MRM mode, and the data included the MRM parent-daughter transition information of the target metabolites, collision energy (CE), declustering potential (DP) and retention time. The use of Skyline software was powerful for metabolite identification and quantification.

Statistical Analysis

Differentially abundant metabolites between the two biological groups were selected using univariate and multivariate analyses. First, orthogonal partial least squares discriminant analysis (OPLS-DA) was conducted to assess the overall differences between the two groups. Then, differentially abundant metabolites were selected based on the variable importance in projection (VIP) values for OPLS-DA, the fold change, and the p values according to univariate analysis. The selection criteria were as follows: 1) VIP value ≥ 1 in the OPLS-DA model, 2) fold change ≥ 1.2 or ≤ 0.8, and 3) p value < 0.05. A volcano plot was generated to visualize the differentially abundant metabolites. Sensitivity, specificity and the area under the receiver operating characteristic curve (ROC) were calculated to evaluate the performance of different metabolites. For expression level clustering analysis of the differentially abundant metabolites, the data were log2 transformed and z-score normalized (zero-mean normalization). For parametric data, Student's *t* test was used for pairwise comparisons between two groups. For nonparametric data, the Kruskal–Wallis test was used. Multiple groups of nonparametric data were compared using one-way analysis of variance (ANOVA). The results are expressed as the mean ± S.E.M. of n observations, where n represents the number of experiments with separate donors. Analyses of the data were conducted using GraphPad Prism 9 software (San Diego, CA). A p value ≤ 0.05 was considered to indicate statistical significance.

Results

The Human Serum Metabolome Was Affected by Active Tuberculosis in Combination with Diabetes Mellitus

To assess the impact of Mycobacterium tuberculosis (*Mtb)* infection on diabetes patients, the metabolites in plasma samples from the DM group and the TB-DM-0 group were analysed first. To identify significant features that differentiated the two groups, an OPLS-DA model was used to avoid overfitting and evaluate the statistical significance of the model. The OPLS-DA score plot showed clear separation between the DM group and the TB-DM-0 group based

on metabolic features (Figure 2A). The permutation test Results of the OPLS-DA model demonstrated strong predictive performance between the DM group and the TB-DM-0 group without overfitting (Figure 2B). To further determine which metabolites were significantly affected by active Mtb, the significant differentially abundant metabolites between the DM group and the TB-DM-0 group were investigated. There were 99 metabolites with different relative abundances between the DM group and the TB-DM-0 group, with 93 upregulated and 6 downregulated metabolites in the TB-DM-0 group compared to those in the DM group (Figure 2C). Clustering analysis of the differentially abundant metabolites between the DM group and the TB-DM-0 group revealed clear differences in their expression patterns (Figure 2D). The four most common differential serum metabolites between TB-DM-0 and DM patients were quinolinic acid, L-histidine, G-ferulic acid and 3-indolepropionic acid (Figure 2E-H).

Screening of Differentially Abundant Metabolites as Potential Biomarkers After Anti-TB Therapy

The standardized regimens for anti-TB treatment recommended by the WHO include four essential medicines designated as first-line treatments: isoniazid (H), rifampicin (R), ethambutol (E) and pyrazinamide (Z). To explore the correlation between HRZE anti-tuberculosis treatment and metabolomics, longitudinal data were obtained from 16 diabetes patients with tuberculosis who received standard treatment. Similarly, the OPLS-DA score plot (Figure 3A) clearly showed separation between the TB-DM-6 group and the TB-DM-0 group. The permutation test demonstrated that the performance of the OPLS-DA model was consistent with the standard parameters between the two groups (Figure 3B). Therefore, this approach can be effectively and reliably applied to detect metabolic profile differences associated with potential prognosis. There were 74 metabolites with different relative abundances between the TB-DM-6 group and the TB-DM-0 group, with 2

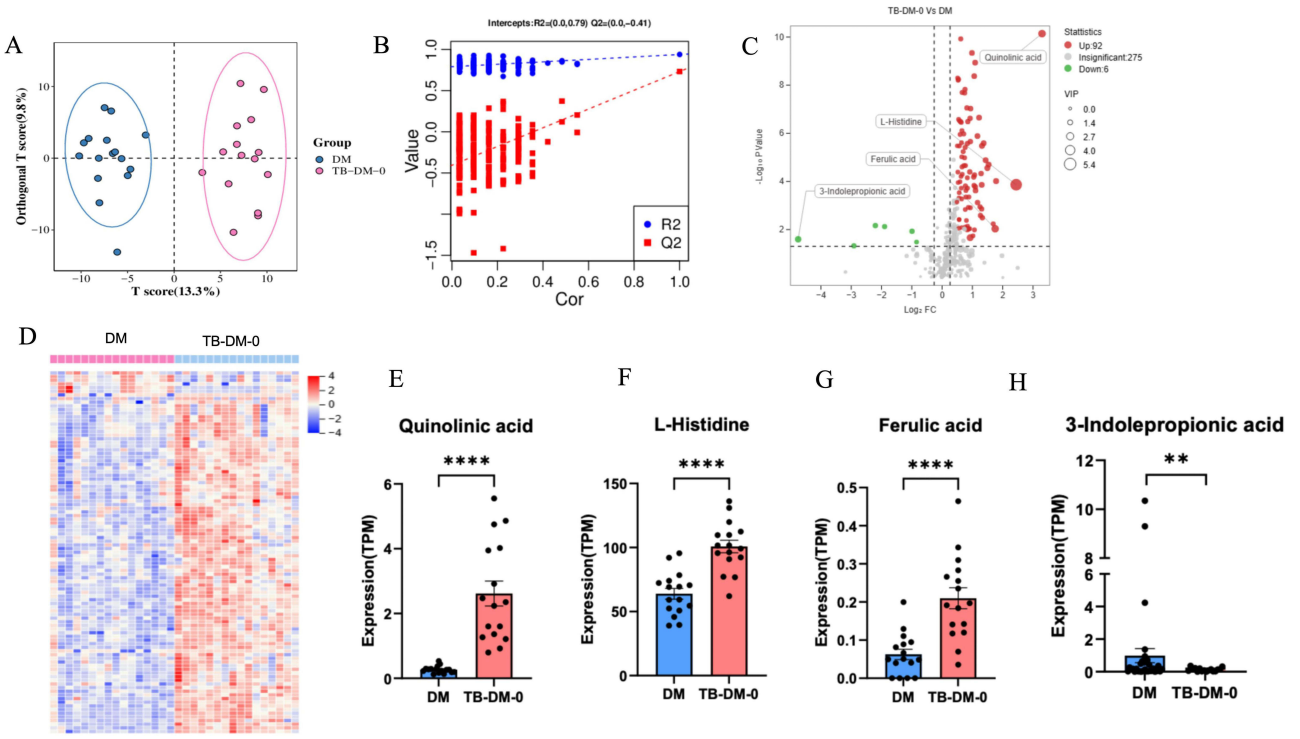

Figure 2 Identification of serum metabolites between the DM and TB-DM-0 groups. The OPLS-DA model for the DM/TB-DM-0 groups (**A**). The permutation test results for the DM/TB-DM-0 groups (**B**). Volcano map of differentially abundant metabolites in the DM/TB-DM-0 groups (**C**). The abscissa is the log2-transformed fold change, and the ordinate is the p value (log10-transformed). Blue is the downregulated significantly different metabolite, red is the upregulated significantly different metabolite, the circle shape is the metabolite with a VIP greater than or equal to 1, the triangle is the metabolite with a VIP less than 1, and the significant metabolite is grey. Clustering of differentially abundant metabolites in the DM/TB-DM-0 group (**D**). Each row represents a differentially abundant metabolite, each column represents a sample, the colour represents the expression level, and the blue to red colour corresponds to the expression level from low to high. Relative abundance of the top 4 differential serum metabolites quinolinic acid (**E**), L-histidine (**F**), G-ferulic acid (**G**) and 3-indolepropionic acid (**H**). The differences among groups were compared using unpaired *t* test **p ≤ 0.01, ****p ≤ 0.001.

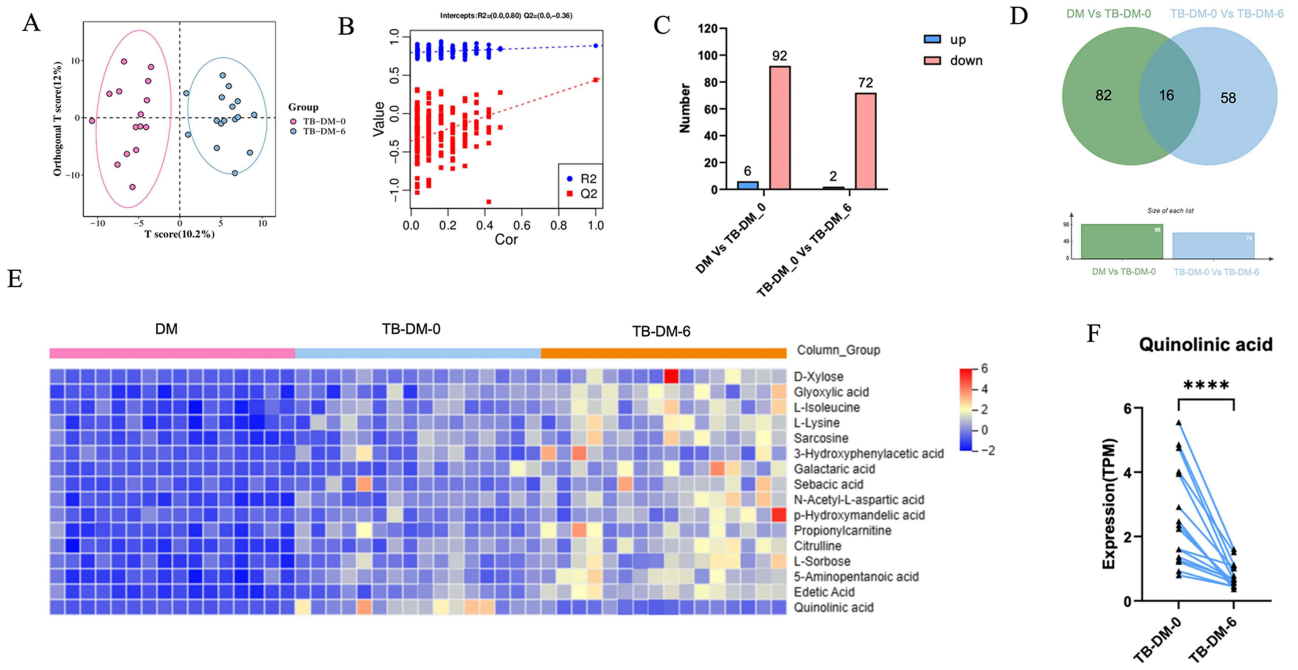

Figure 3 Differentially abundant metabolites identified as potential biomarkers after anti-TB therapy. The OPLS-DA model for the TB-DM-0/TB-DM-6 groups (**A**). The permutation test results for the TB-DM-0/TB-DM-6 groups (**B**). Quantitative plot of differentially abundant metabolites (DM vs TD0 and TD-6 vs TD0) (**C**). Venn diagram of metabolites in the TD-0 group compared with those in the other two groups (**D**). Clustering of differentially abundant metabolites in the DM, TB-DM-0 and TB-DM-6 groups (**E**). Relative abundance of quinolinic acid (**F**). The differences among groups were compared using unpaired *t* test ****p ≤ 0.001.

upregulated and 72 downregulated metabolites in the TB-DM-0 group compared to the TB-DM-6 group (Figure 3C). A comparison of the TB-DM-0 group with the other two groups (DM vs TB-DM-0 and TB-DM-6 vs TB-DM-0) showed that the relative amount of 16 overlapping metabolites in the serum of the TB-DM-0 patients changed dramatically (Figure 3D). Table 2 shows the 16 differentially abundant metabolites between the three groups. Clustering analysis of the differentially abundant metabolites between the three groups (DM, TB-DM-0 and TB-DM-6) revealed clear differences in their expression patterns (Figure 3E). Quinolinic acid was the top differential serum metabolite between TB-DM-0 and TB-DM-6 patients (Figure 3F).

To further explore the clinical potential of the significantly altered metabolites in this study, the discriminatory ability of the differentially abundant metabolite QA was evaluated using receiver operating characteristic (ROC) curves. QA showed good efficacy in distinguishing between the DM group and the TB-DM-0 group, with an AUC of 1.0 (95% CI 1–1) (Figure 4A). Similarly, we aimed to identify differentially abundant metabolites as potential biomarkers for assessing the efficacy of anti-tuberculosis treatment. The ROC curve for QA for distinguishing between the TB-DM-6 group and the TB-DM-0 group is shown in Figure 4B, with an AUC of 0.93 (95% CI 0.85–1) for this differentially abundant metabolite. QA performed well in distinguishing between the DM group and the TB-DM-0 group and between the TB-DM-6 group and the TB-DM-0 group. Compared to that in diabetic patients, the level of QA was significantly greater in TB-DM patients (Figure 2E) and decreased significantly after antituberculosis treatment (Figure 3F), approaching the levels observed in patients with diabetes alone.

Other differentially abundant metabolites, such as D-xylose, were effective at distinguishing between the DM group and the TB-DM-0 group, with an AUC of 0.97 (95% CI 0.93–1) (Supplementary Figure 1A). However, the ROC curve for distinguishing between the TB-DM-6 group and the TB-DM-0 group was not sufficient, with an AUC of 0.73 (95% CI 0.55–0.92) (Supplementary Figure 1B). Compared to that in diabetic patients, D-xylose was significantly elevated in TB-DM patients (Supplementary Figure 1C) but did not decrease significantly after antituberculosis treatment (Supplementary Figure 1D).

Table 2 Top 16 Differential Serum Metabolites Between TB-DM-6 Patients and DM Patients Compared to TB-DM-0 Patients

No.	Name_des	DM/TB-DM-0			TB-DM-6/TB-DM-0		
		Fold Change	*p* value	VIP	Fold Change	*p* value	VIP
1	D-Xylose	0.566389	8.79E-08	1.527947	0.59641	0.012879	1.2184
2	Glyoxylic acid	0.676461	0.000295	1.151831	0.729897	0.000967	1.118792
3	L-Isoleucine	0.693831	0.000111	1.07096	0.739163	0.000757	1.032459
4	L-Lysine	0.637604	9.58E-06	1.196836	0.779804	0.006143	1.02568
5	Quinolinic acid	0.101625	7.18E-11	2.988001	3.353083	7.55E-06	2.225727
6	Sarcosine	0.663783	0.000103	1.132974	0.72194	0.001266	1.301223
7	3-Hydroxyphenylacetic acid	0.477158	0.010271	1.237906	0.649981	0.04842	1.106617
8	Galactaric acid	0.562866	0.009969	1.776352	0.526673	0.000424	1.705326
9	Sebacic acid	0.573157	0.004195	1.116174	0.644407	0.0076	1.223283
10	N-Acetyl-L-aspartic acid	0.663099	1.12E-06	1.204964	0.765796	0.001415	1.026479
11	p-Hydroxymandelic acid	0.681333	0.008885	1.053173	0.55936	0.003499	1.472783
12	Propionylcarnitine	0.586936	0.000155	1.410339	0.720684	0.005163	1.088911
13	Citrulline	0.673987	3.38E-06	1.199127	0.763295	0.000409	1.084555
14	L-Sorbose	0.697534	4.11E-05	1.161463	0.743984	0.001281	1.240153
15	5-Aminopentanoic acid	0.635224	7.83E-07	1.314069	0.763723	0.000143	1.069178
16	Edetic Acid	0.35517	2.78E-05	1.976812	0.550441	1.25E-05	1.980524

The Trend of QA in TB-Only Patients Was Consistent with That in TB-DM Patients

We analysed the metabolites of tuberculosis-only patients and healthy individuals. Consistent with the results for TB-DM, quinolinic acid (QA) levels were significantly elevated in the tuberculosis-only group and decreased significantly after antituberculosis treatment (TB-6), approaching the levels observed in healthy individuals (Figure 5A). QA also demonstrated good discriminatory power in distinguishing between the healthy group and TB-0 patients, with an AUC of 0.92 (95% CI 0.85–1) (Figure 5B). Likewise, QA exhibited good discriminatory power in distinguishing between the TB-0 and TB-6 groups, with an AUC of 0.88 (95% CI 0.78–0.96) (Figure 5C).

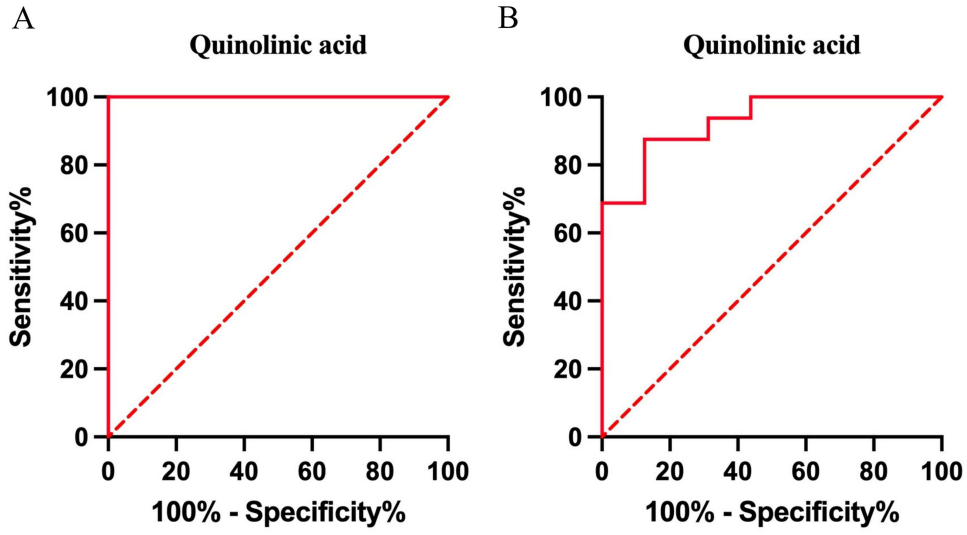

Figure 4 ROC curves and relative abundance of QA. QA distinguished TB-DM from DM patients well (AUC = 1) (**A**). QA could also distinguish TB-DM-0 patients from TB-DM-6 patients (AUC = 0.9297) (**B**).

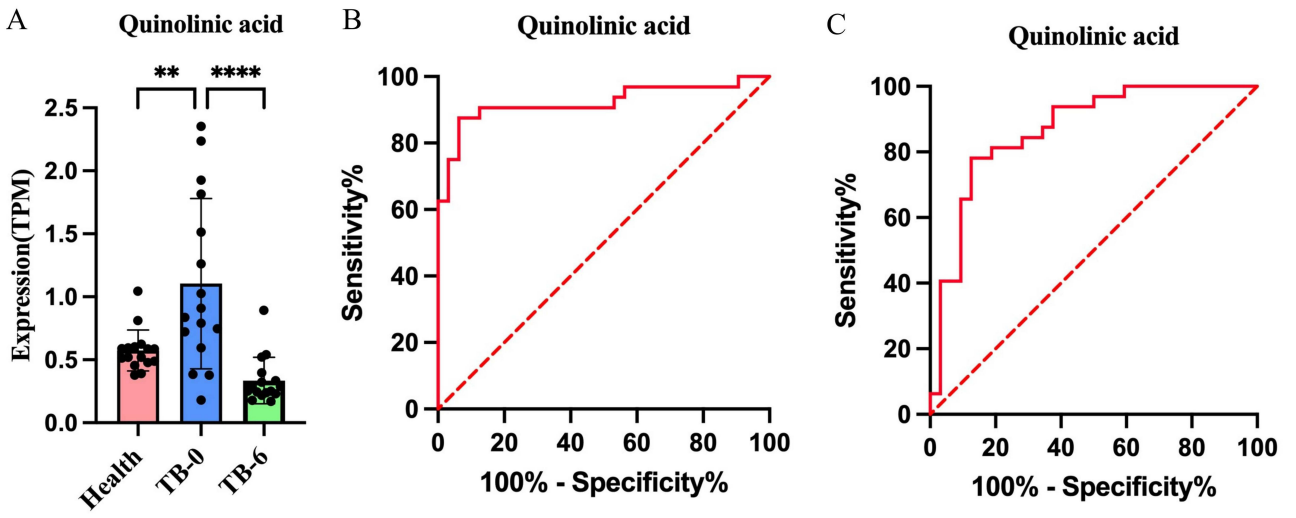

Figure 5 Screening of differentially abundant metabolites in TB patients. Relative abundance of QA (**A**). QA showed good efficacy in distinguishing between healthy individuals and TB patients (**B**). Moreover, QA could distinguish untreated TB patients from cured TB patients (**C**). The differences among groups were compared using unpaired *t* test **p ≤ 0.01, ****p ≤ 0.001.

Discussion

Early detection and intervention are crucial for effective tuberculosis control. Mycobacterial culture is considered the gold standard for diagnosing tuberculosis.[23] However, there is currently no unified laboratory standard for assessing tuberculosis treatment outcomes, and tuberculosis treatment relies mainly on sputum smear microscopy and mycobacterial culture.[24] Traditional culture methods have limitations, such as difficulty in obtaining sputum samples, long incubation times, low positivity rates, and inconsistent sputum quality.[25] Therefore, the WHO strongly advocates for no sputum-based methods for diagnosing and treating tuberculosis.[26] Plasma samples have advantages over sputum samples in terms of easier collection and storage, and an increasing number of tuberculosis biomarkers have been detected in blood. Thus, screening for new treatment response markers through metabolomic analysis may provide unified diagnostic criteria for active tuberculosis and treatment response in tuberculosis patients.

Diabetes patients exhibit impaired innate and adaptive immune functions, leading to increased susceptibility to Mtb infection, as well as a higher risk of treatment failure with anti-tuberculosis drugs and increased mortality.[27] Diabetes patients have an increased susceptibility to tuberculosis, characterized by compromised immune mechanisms including reduced host recognition of Mtb, decreased activity of phagocytic cells, reduced production of chemotactic factors and cytokines, decreased numbers of immune cells, alterations in cytokine levels and changes in cell factor levels, making it easier for Mtb to disseminate in the body.[28]

Diabetes patients also have specific metabolic changes that impair host immune protective effects, thereby facilitating Mtb infection, disease progression, and exacerbation. Glycemic control directly impacts disease development and outcomes.[29] Research indicates certain metabolic pathways, particularly genes involved in fatty acid and protein degradation metabolism, significantly correlate with tuberculosis progression.[30] Additionally, baseline levels of glucose, glycosylated haemoglobin, triglycerides, high-density lipoprotein cholesterol, lipoproteins, and hormones collectively create a conducive environment in comorbid patients, aiding Mtb survival and lesion dissemination. Studies also link tuberculosis comorbidity with diabetes and vitamin deficiencies.[31]

Therefore, metabolomics and lipidomic can collectively capture the significant changes in carbohydrate and amino acid metabolism induced by *Mtb* infection and identify host–pathogen interactions in this disease. QA is a dicarboxylic acid and a downstream product of the tryptophan pathway which was found to be highly regulated in various stages of TB infection and disease through high-resolution metabolomics and unbiased pathway analysis.[17] This regulation was characterized by increased breakdown of tryptophan, which could be reversed by effective treatment for active TB, indicating an adaptation to bacterial clearance. In a study on tryptophan-targeted metabolomics, increased levels of QA

were found in the serum of TB patients compared to patients with other lung diseases, ranking among the top 12 out of 400 detected small-molecule metabolites.[32] These findings are consistent with our research, which showed significant increases in QA after *Mtb* infection. QA is also associated with tumour diseases. In patients with non-small cell lung cancer receiving a PD-1 inhibitor, lower QA concentrations were significantly correlated with improved overall survival.[33] QA serves as a metabolic checkpoint in glioblastoma by triggering NMDA receptor activation and Foxo1/PPARγ signalling in macrophages, leading to a tumour-supportive phenotype.[34]

Previous research has developed biomarkers for tuberculosis diagnosis, treatment success, relapse, or failure, but these biomarkers have not included individuals with coexisting diabetes mellitus, especially in the absence of posttreatment follow-up information.[35] Compared with those in TB-only patients, both innate and adaptive immune responses are affected in TB-DM patients. In TB-only patients, peripheral immune responses typically return to normal levels after successful treatment. In contrast, TB-DM patients exhibit heightened inflammatory responses and a delayed response to tuberculosis treatment, with inflammation-related cytokines in plasma remaining elevated even after treatment completion.[36,37] Several transcriptomic studies have shown extensive changes in gene expression in the blood of tuberculosis patients compared to healthy individuals, with enhanced circulating inflammatory responses. These transcriptomic features rapidly decrease with successful tuberculosis treatment, significantly decrease after 2 months of treatment and mostly disappear at 12 months. However, the overall gene expression in the TB-DM group differed from that in the TB-only group at various time points. The overall gene expression changes throughout antituberculosis treatment are minimal, remaining at high levels even at the end of tuberculosis treatment and persisting up to 12 months postdiagnosis.[38]

In this study, targeted metabolomic analysis of plasma from patients with diabetes mellitus (DM) and tuberculosis-diabetes mellitus (TB-DM) was conducted to identify metabolic features specific to TB-DM patients. We found that the biomarker QA performed well in distinguishing DM patients from TB-DM patients. QA levels were significantly elevated in TB patients and decreased significantly after anti-tuberculosis treatment. These studies suggest that QA is a potential diagnostic biomarker and therapeutic target for TB-DM patients.

Limitations

However, our study has several limitations. First, we did not include patients who experienced treatment failure because the patients included in our cohort and follow-up showed good treatment outcomes. Second, our sample size was relatively small. In future studies, we plan to include larger multicentre populations and individuals with a higher risk of treatment failure to further validate the treatment response assessment. Additionally, we aim to conduct more in-depth basic research to elucidate the mechanisms underlying the elevation of QA after *Mtb* infection and its role in the development of tuberculosis.

Conclusion

In summary, we identified differences between diabetic patients and untreated TB-DM patients as well as between untreated TB-DM patients and TB-DM patients after completion of treatment. QA may serve as a specific diagnostic biomarker and therapeutic target for TB-DM patients.

Data Sharing Statement

The datasets generated analysed during the current study are not publicly available due other parts of some data are still being analysed but are available from the corresponding author on reasonable request.

Ethics Approval

The study was approved by the Ethics Committee of the Third People's Hospital of Shenzhen (number: 2021-014-02). This study was performed in compliance with the Declaration of Helsinki.

Consent to Participate

Written informed consent was obtained from all participants before sample collection.

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Disclosure

The authors declare that they have no competing interests in this work.

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