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Correlation of Serum C-reactive Protein, IL-6, Blood Lipid and Blood Glucose in Patients with Type 2 Diabetes Mellitus Complicated with Pulmonary Tuberculosis

Chunjing Gao[a], Meng Zhao[b], Yunshi Zhang[a], Shan Zhao[a], Liandong Zong[a], Zongwei Kan[a*]

Abstract

Objective: To explore the correlation of serum C-reactive protein, IL-6, blood lipid and blood glucose in patients with type 2 diabetes mellitus (DM) complicated with pulmonary tuberculosis (PTB). Methods: In this experiment, 74 patients with DM complicated with PTB admitted to our hospital from March 2016 to April 2019 (research group, RG) and 30 cases of healthy physical examination at the same time (control group, CG) were collected as study objects. The expressions of C-reactive protein, IL-6, blood glucose and blood lipid were observed in patients with DM complicated with PTB. The predictive value of C-reactive protein, IL-6, blood glucose and blood lipid in DM complicated with PTB was analyzed. The correlation of clinical pathology of DM complicated with PTB was analyzed. The correlation between the expression levels of C-reactive protein, IL-6 and blood glucose, blood lipid was observed. Results: The expression of each index in RG was significantly higher than that in CG ($P < 0.05$). According to ROC curve analysis, the area under C-reactive protein curve, IL-6 curve, FPG curve, HbAlc curve, TC curve, LDL-C curve and HDL-C curve were 0.628, 0.767, 0.742, 0.780, 0.737, 0.726 and 0.721 respectively. The expression levels of C-reactive protein and IL-6 were closely related to cough, hemoptysis and staging of patients with DM complicated with PTB ($P < 0.05$). Pearson test showed that C-reactive protein was positively correlated with blood glucose ($r = 0.655$, $p < 0.001$), and IL-6 was positively correlated with blood glucose ($r = 0.567$, $p < 0.001$). Conclusion: C-reactive protein, IL-6, blood lipid and blood glucose are abnormally expressed in patients with DM complicated with PTB. C-reactive protein, IL-6, blood lipid and blood glucose may be involved in the development and progression of DM complicated with PTB, which is expected to be an excellent index for the diagnosis and treatment of DM complicated with PTB in the future.

Keywords: diabetes mellitus (DM), pulmonary tuberculosis (PTB), serum C-reactive protein

Introduction

Diabetes mellitus (DM) is the most common chronic disease in the world at present, which develops mostly in middle-aged and elderly people. Since the 19th century, the incidence of DM has remained high. More data (Inzucchi et al,2015) show that the incidence of DM is increasing year by year with the development of society and the improvement of people's living standards in recent years. According to the statistics of Zinman et al. (Zinman et al ,2015), the number of DM patients in the world has exceeded 400 million in 2015, and the number of patients in China ranks first in the world. The treatment of DM is extremely difficult, and clinical scholars have been trying to find an effective means

[a]Department of Tuberculosis, Xuzhou Infectious Disease Hospital, Xuzhou221004, Jiangsu Province, China.
[b]Department of Endocrinology, Affiliated Hospital of Xuzhou Medical University, Xuzhou221004, Jiangsu Province, China.
**Corresponding Author: Zongwei Kan*
Email: kzwei1981@126.com

to prevent and treat DM, but so far, they have not made a significant breakthrough (Carlsson et al,2015). DM can easily cause many complications, such as cardio-cerebrovascular disease, neurological diseases, nephrosis, etc. Once the disease takes a turn for the worse without timely treatment, it will directly lead to malignant tumor diseases. DM is prone to tuberculous infection, the most common of which is tuberculosis (Kumar et al,2015). According to the statistical results of Ronacher et al. (Ronacher et al,2015), about 26.75% of diabetic patients are complicated with tuberculosis, and the older the patients are, the higher the risk is. The DM accelerates the development of PTB, which is more likely to deteriorate into lung cancer, but the PTB increases the drug resistance of DM and becomes more difficult to treat (Chiang et al,2015). The two diseases form a vicious circle, so it has become a hot research target which needs to be solved in clinical practice at present.

C-reactive protein refers to some proteins (acute proteins) that increase sharply in plasma when the body is infected or tissue is damaged. C-reactive protein can activate complement and enhance phagocytosis of phagocytes to play a conditioning role, thus eliminating pathogenic microorganisms that invade the body and damaged, necrotic and apoptotic tissue cells, so it plays a crucial protective role in the natural immunity process of the body (Sproston et al,2018; Badimon and Peña,2018). In the process of infection, the body is also stimulated by many cytokines (Liu et al,2018; Majewski and Agier,2018). Interleukin occupies a dominant position in cytokines. Interleukin is a kind of cytokine which is produced by many kinds of cells and reacts to many kinds of cells. Cytokines can regulate the growth, differentiation and other function of immunity system cells. Interleukin-6 (IL-6) belongs to IL family, which is mainly secreted by activated dendritic cells and plays a crucial role in the regulation of immune response (Sun et al,2015). This research aimed to explore the correlation and clinical significance between these indexes and DM complicated with PTB by detecting the expression of C-reactive protein, IL-6, blood lipid and blood glucose in blood of patients with DM complicated with PTB.

Materials and methods:

1.1 Baseline data

In this experiment, 74 patients with DM complicated with PTB admitted to our hospital from March 2016 to April 2019 (RG) and 30 cases of health physical examination at the same time (CG) were collected as study objects. The average age of patients in RG was (49.4±9.6) years old and that of patients in CG was (48.24±10.2) years old. This experiment has been ratified by the Medical Ethics Committee of our hospital.

1.2 Inclusion and exclusion criteria

Inclusion criteria: Patients conformed to the diagnosis guidelines for DM and tuberculosis issued in 2014(Dabelea et al,2014; Menzies and Cohen,2012); They were diagnosed and treated in our hospital; They had full case data; They agreed to cooperate and participate in the investigation of our hospital; Their ages ranged from 30 to 65; There were no other severe organ diseases affecting this research; The informed consent form was affixed by the patient or his/her immediate dependents.

Exclusion criteria were as follows: the patient who died during treatment; comorbid with other tumors; complicated by other cardio-cerebrovascular diseases; physical disabilities; pregnancy; complicated by other autoimmune diseases; complicated by other chronic diseases; the patient who diverted to other hospital; surgical contraindications; mental disorders; language disturbance and diseases affecting the results of this research.

1.3 Main reagents

C-reactive protein kit was purchased from AmyJet Scientific Inc, and the item number was HK358. IL-6 kit was from Beijing Solarbio Science & Technology Co., Ltd., and the number was SEKH-0013. KH19A desktop high-speed and high-performance centrifuge was purchased from KAIDA Company. The low-temperature refrigerator (-80℃) was purchased from ThermoFisher Scientific, USA. The automatic biochemical analyzer was purchased from Jiaozuo Road Feifan Biotechnology Co., Ltd., and the item number was LFF-LC-1781.

1.4 Detection methods

The fasting venous peripheral blood (5mL) was collected from patients and healthy cases in the morning. After standing for 30min at room temperature, the blood was centrifuged for 10min (3000rpm/min) to obtain the upper serum. The serum was separately packaged with enzyme-free EP tubes, part of which was taken for experiment, and the rest was stored at -80℃. The blood sugar function (fasting blood sugar FPG, glycosylated hemoglobin HbAlc) and serum lipid function (serum total cholesterol TC, low density lipoprotein-cholesterol LDL-C, high density lipoprotein-cholesterol HDL-C) were tested by automatic biochemical analyzer. The C-reactive protein and IL-6 were tested by ELISA. The operation was conducted in strict accordance with the kit specifications.

1.5 Outcome measures

Main outcome measures: The expressions of C-reactive protein, IL-6, blood sugar and serum lipid were observed in patients with DM complicated with PTB. The predictive value of C-reactive protein, IL-6, blood sugar and serum lipid in DM complicated with PTB was analyzed Secondary outcome measures: The correlation of clinical pathology of DM complicated with PTB was analyzed. The relativity between the expression levels of C-reactive protein, IL-6 and blood glucose, blood lipid was observed.

1.6 Statistical analysis

In this research, SPSS20.0 was applied to statistically analyse the collected data, and GraphPad 7 was applied to plot the required pictures. K-S test was applied to analyse the distribution of dose data, in which normal distribution data were represented by mean number ± standard deviation (Meas±SD). The independent-samples T test was applied for comparison between groups. The paired t-test was used for comparison within groups. The one-way ANOVA was applied for comparison among groups, which was represented by F. The counting data were represented as a percentage (%) and tested by chi-square test, which was expressed by χ^2. ROC was used to draw the predictive value of C-reactive protein, IL-6 and blood sugar and serum lipid in patients with DM complicated with PTB. The survival rate was computed by Kaplan-Meier, and the survival rate was compared by Log-rank test. There were statistical differences with $P < 0.05$.

Results

2.1 Baseline data

There was no obvious difference between the RG and the CG in terms of age, BMI, smoking history, drinking history, place of residence, marital status, exercise habit and course of disease, which proved to be comparable ($P > 0.05$). (Table 1)

Table 1. **Basic clinical data [n (%)]**

	RG (n=74)	CG (n=30)	χ^2 or t	P
Age/years old	49.4±9.6	48.7±10.2	0.741	0.331
BMI	21.23±4.86	21.16±5.02	0.066	0.948
Smoking history				
Yes	48 (64.86)	18 (60.00)	0.218	0.641
No	26 (35.14)	12 (40.00)		
Drinking history				
Yes	19 (25.68)	9 (30.00)	0.203	0.652
No	55 (74.32)	21 (70.00)		
Place of residence				

City	54 (72.97)	23 (76.67)	0.152	0.697
Rural	20 (72.03)	7 (23.33)		
Marital status				
Married	69 (93.24)	27 (90.00)	0.316	0.574
Unmarried	5 (6.76)	3 (10.00)		
Exercise habit				
Yes	31 (7.32)	11 (0.00)	0.242	0.623
No	43 (92.68)	19 (100.00)		
Course of disease (week)	3.74±1.04	3.92±0.86	0.838	0.404

2.2 Expression of C-reactive protein, IL-6, blood sugar and serum lipid in patients with DM complicated with PTB

In RG, the expressions of C-reactive protein, IL-6, FPG, HbAlc, TC, LDL-C, HDL-C were 28.24±25.67 (mg/L), 126.09±31.49 (pg/mL), 11.54±1.28 (mmol/L) , 11.03±1.18 (%), 5.48±1.27 (mmol/L), 4.18±1.19 (mmol/L) and 1.68±0.43 (mmol/L) respectively. In CG, the expressions of C-reactive protein, IL-6, FPG, HbAlc, TC, LDL-C, HDL-C were 4.28±2.31 (mg/L), 24.26±3.21 (pg/mL), 6.13±0.35 (mmol/L) , 7.15±0.34 (%), 3.93±0.62 (mmol/L), 1.95±0.84 (mmol/L) and 0.75±0.42 (mmol/L) respectively. The expression of each index in RG was obviously higher than that in CG ($P < 0.05$). (Figure 1).

2.3 Predictive value of C-reactive protein, IL-6, blood glucose and blood lipid in DM complicated with PTB

ROC was plotted according to the expressions of C-reactive protein, IL-6 and blood glucose and blood lipid. The results showed that the area under C-reactive protein curve, IL-6 curve, FPG curve, HbAlc curve, TC curve, LDL-C curve and HDL-C curve were 0.628, 0.767, 0.742, 0.780, 0.737, 0.726 and 0.721 respectively. (Table 2, Figure 2)

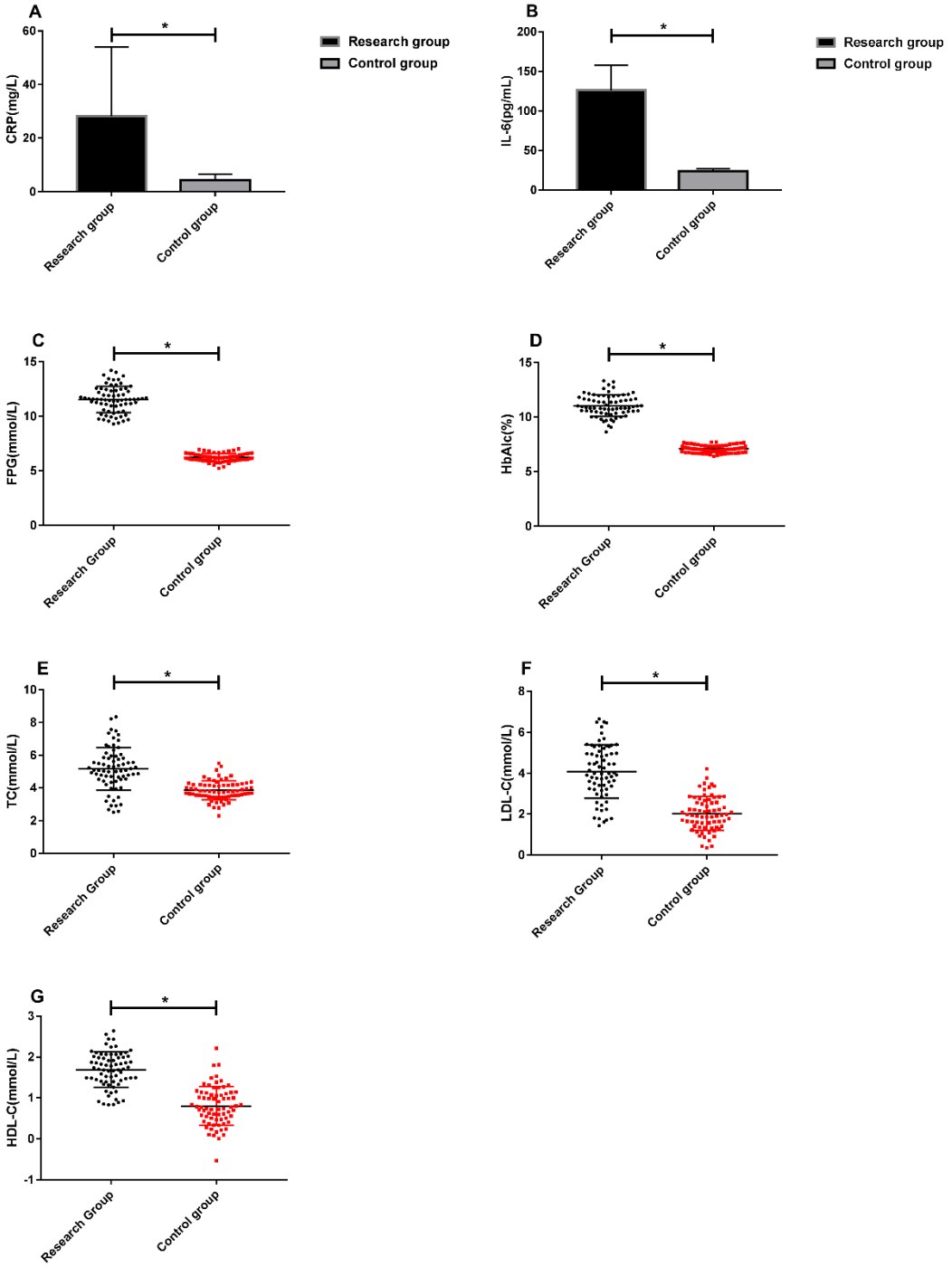

Figure 1. **Expression of C-reactive protein, IL-6, blood glucose and blood lipid in patients with DM complicated with PTB**

A, Expression level of C-reactive protein.
B, Expression level of IL-6.
C, Expression level of FPG.
D, Expression level of HbAlc.
E, Expression level of TC.
F, Expression level of LDL-C.
G, Expression level of HDL-C.
Note: The symbol * indicates a difference in comparison between the two groups ($P < 0.05$).

Table 2. **ROC curve**

Indicators	AUC	95%CI	Sensitivity	Specificity	Std. Error	Cut-off
C-reactive protein	0.628	0.519~0.737	83.33%	44.59%	0.056	35.390
IL-6	0.767	0.655~0.879	66.67%	87.84%	0.057	10.070
FPG	0.742	0.654~0.831	73.77%	69.01%	0.045	6.349
HbAlc	0.780	0.701~0.859	60.66%	83.10%	0.040	7.440
TC	0.737	0.647~0.826	63.93%	81.69%	0.046	4.924
LDL-C	0.726	0.640~0.812	73.77%	66.20%	0.044	2.238
HDL-C	0.721	0.633~0.808	68.58%	69.01%	0.045	1.018

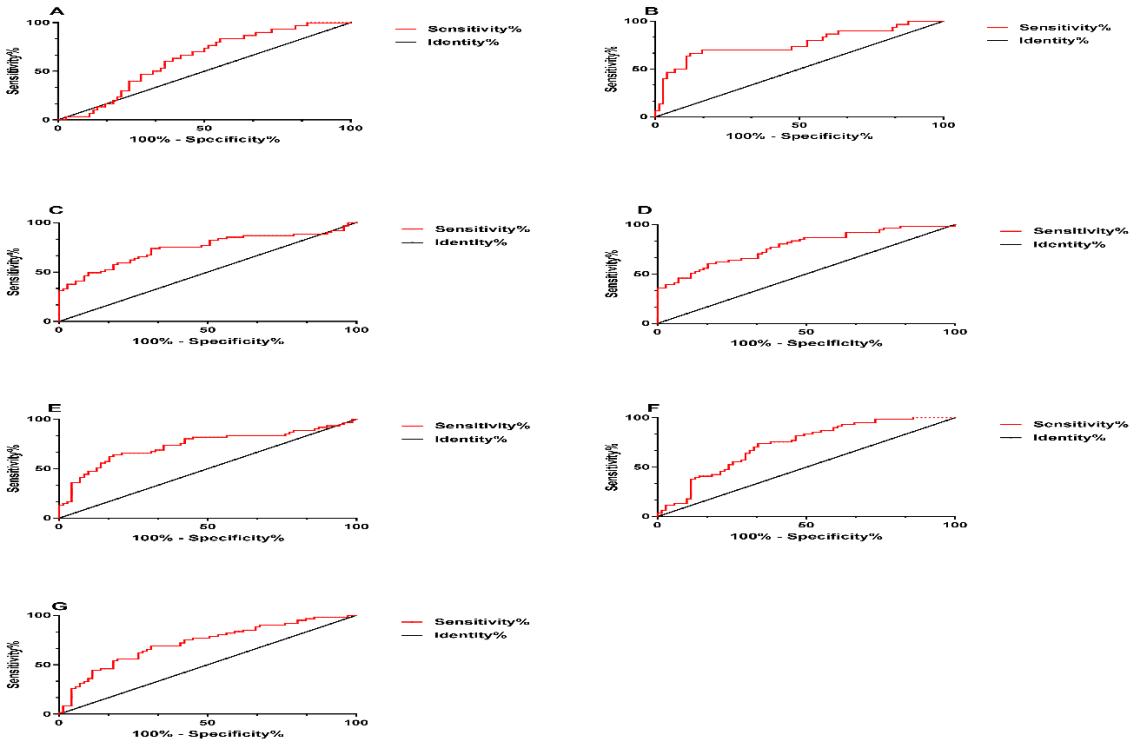

Figure 2. **ROC curve**

A, When the cut-off value was 35.390, the sensitivity and specificity of C-reactive protein were 83.33% and 44.59% respectively. B, When the cut-off value was 10.070, the sensitivity and specificity of IL-6 were 66.67% and 87.84% respectively. C, When the cut-off value was 6.349, the sensitivity and specificity of FPG were 73.77% and 69.01% respectively. D, When the cut-off value was 7.440, the sensitivity and specificity of HbAlc were 60.66% and 83.10% respectively. E, When the cut-off value was 4.924, the sensitivity and specificity of TC were 63.93% and 81.69% respectively. F, When the cut-

off value was 2.238, the sensitivity and specificity of LDL-C were 73.77% and 66.20% respectively. G, When the cut-off value was 1.018, the sensitivity and specificity of HDL-C were 68.58% and 69.01% respectively. exercise habit in patients with DM combined with PTB (P > 0.05), but they were closely correlated with cough, hemoptysis and staging in patients with DM combined with PTB (P < 0.05). (Table 3, Table 4)

2.4 Correlation analysis of clinical pathology of DM complicated with PTB

The C-reactive protein and IL-6 were not obviously correlated with age, smoking, course of disease and

Table 3. **Correlation analysis between expression level of C-reactive protein in RG and clinical pathology of patients**

	n	C-reactive protein	t or F	P
Age				
≤ 49	45	28.24±25.67	0.039	0.969
＞ 49	29	28.52±25.49		
Smoking				
Yes	48	28.18±25.75	0.032	0.975
No	26	27.98±25.67		
Coughing				
Yes	47	35.97±25.87	2.007	0.049
No	27	23.58±25.02		
Course of disease				
＞5	49	28.13±25.24	0.029	0.977
≤5	25	28.31±25.19		
Hemoptysis				
Yes	32	35.89±25.73	2.138	0.036
No	42	23.15±25.13		
Staging				
Progressive stage	19	29.24±25.63		
Improvement period	24	18.12±21.33	8.029	0.007
Stationary phase	31	8.28±5.31		
Exercise habit				
Yes	19	28.22±25.63	0.001	0.100
No	55	28.21±25.52		

Table 4. **Correlation analysis between expression level of IL-6 in RG and clinical pathology of patients**

	n	IL-6	t or F	P
Age				
≤ 49	45	126.09±31.49	0.032	0.975
＞ 49	29	126.32±31.53		
Smoking				
Yes	48	127.02±30.19	0.066	0.948
No	26	126.53±31.22		
Coughing				
Yes	47	135.59±33.49	2.081	0.041
No	27	119.33±30.25		
Course of disease				
＞5	49	126.07±31.29	0.009	0.993
≤5	25	126.14±31.33		
Hemoptysis				
Yes	32	136.75±34.12	2.097	0.040
No	42	119.98±34.05		
Staging				
Progressive stage	19	126.09±31.49		
Improvement period	24	85.33±25.31	128.200	0.001
Stationary phase	31	27.26±6.21		
Exercise habit				
Yes	19	126.03±30.92	0.068	0.946
No	55	126.59±31.22		

2.5 Correlation between the expression levels of C-reactive protein, IL-6 and blood glucose

Pearson test showed that C-reactive protein was positively correlated with blood glucose ($r = 0.655$, $p < 0.001$), and IL-6 was positively correlated with blood glucose ($r = 0.567$, $p < 0.001$). (Table 5, Figure 3)

Table 5 Pearson correlation

	miR-152	IL-6
r	0.655	0.567
95%CI	0.543~0.745	0.426~0.681
P	0.001	0.001

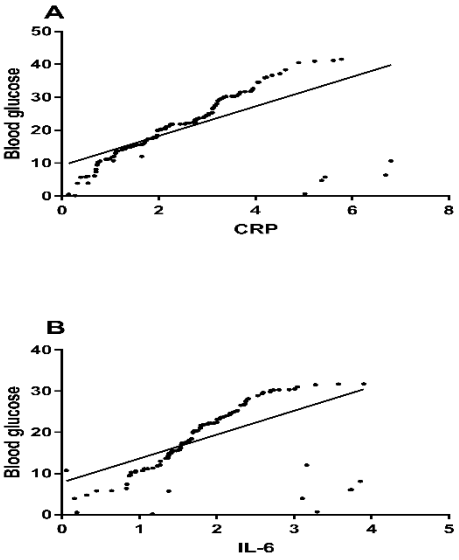

Figure 3. **Pearson correlation**

A, Correlation between C-reactive protein and blood glucose.

B, Correlation between IL-6 and blood glucose.

Discussion

DM is defined as a group of metabolism diseases, which is characterized by hyperglycaemia caused by insulin secretion deficiency, insulin action or both. In 2014, the morbidity of DM was estimated to be 9% in the world, and nearly 1.6 million people died of DM in 2015. DM is also bound up with a high incidence of many complications, such as nephropathy retinopathy, nephrosis, neuropathies and cardio-vascular diseases. The prophylaxis and management of these complications have become the main directions of modern diabetes care. The most typical manifestation of diabetic patients is the damage of immune system, which greatly increases the risk of being infected by MTB and leads to the occurrence of PTB (Collins et al,2015). PTB is a chronic infection disease caused by mycobacterium tuberculosis, which can attack many organs. PTB is the most common infection, and the excretors are the important infection sources (LoBue et al,2017). Its main clinical manifestations are low fever, night sweat, fatigue, anorexia, cough, expectoration, hemoptysis, chest pain, chest distress or dyspnea to varying degrees, which has a severe impact on the quality of life of patients. A great number of studies suggest (Ossalé et al,2018; Garfin and Mantala,2017) that early diagnosis and appropriate treatment are the important research directions at present.

At present, the clinical indexes for detecting DM are generally blood sugar function (FPG, HbAlc) and serum lipid function (TC, LDL-C, HDL-C). Inflammation is the main characteristic of PTB patients in intensive care unit. As a member of IL family, IL-6 is mainly secreted by activated antigen presenting cells, which plays a crucial role in the proliferation of T lymphocyte 17 and also participates in the process of autoimmune diseases (Liu et al,2018; Jiang and Deng,2016). C-reactive protein is a kind of acute inflammatory protein, which is highly expressed when the patient was infected with inflammation. It can be irreversibly dissociated into five independent monomers, called monomer C-reactive protein, at the site of inflammation and infection (Boras et al,2014). We suspected that C-reactive protein and IL-6 were closely related to the development and progression of DM complicated with PTB. Therefore, we studied C-reactive protein, IL-6, blood glucose and blood lipid, and the findings revealed that the expressions of C-reactive protein, IL-6, FPG, HbAlc, TC, LDL-C and HDL-C in serum of patients with DM complicated with PTB were significantly higher than those of healthy cases, which indicated that C-reactive protein, IL-6, FPG, HbAlc, TC, LDL-C and HDL-C were closely related to the development and progression of DM complicated with PTB. By drawing ROC, the results showed that the area under C-reactive protein curve, IL-6 curve, FPG curve, HbAlc curve, TC curve, LDL-C curve and HDL-C curve were 0.628, 0.767, 0.742, 0.780, 0.737, 0.726 and 0.721 respectively, and they all had better sensitivity and specificity. This indicated that C-reactive protein, IL-6, FPG, HbAlc, TC, LDL-C and

HDL-C could be applied as prediction indexes of DM complicated with PTB.

By analyzing the differences of C-reactive protein and IL-6 in clinical pathology of patients with DM complicated with PTB, it was found that the C-reactive protein and IL-6 were not obviously correlated with age, smoking, course of disease and exercise habit in patients with DM combined with PTB, but they were closely correlated with cough, hemoptysis and staging in patients with DM combined with PTB. The severity of the disease can be determined by detecting the expression levels of C-reactive protein and IL-6. The Pearson correlation analysis revealed that the expression levels of serum C-reactive protein and IL-6 were positively correlated with blood glucose and blood lipid.

We have preliminarily proved the clinical value of C-reactive protein, IL-6, blood lipid and blood glucose through the above research, but there are still some limitations in this study. First of all, there is no basic cell experiment in this study. Secondly, our experimental sample base is small and the population is relatively single. Therefore, we hope to supplement our research results by carrying out basic cell experiments and expanding the sample size of research objects in future studies.

To sum up, C-reactive protein, IL-6, blood lipid and blood glucose are abnormally expressed in patients with DM complicated with PTB. C-reactive protein, IL-6, blood lipid and blood glucose may be involved in the development and progression of DM complicated with PTB, which is expected to be an excellent index for the diagnosis and treatment of DM complicated with PTB in the future.

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