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The Effect of Tuberculosis Infection on Pancreatic Beta-Cell Function in Patients with Type 2 Diabetes Mellitus

Mengdan Kong[1], Ailin Zhong[2], Shilin Qu[3], Junli Xue[1*]

[1]Department of Endocrinology, Jingzhou Hospital Affiliated to Changjiang University, Jingzhou, China
[2]Department of Tuberculosis, The First People's Hospital of Jingzhou City, Jingzhou, China
[3]Department of Endocrinology, The Third People's Hospital of Jingzhou City, Jingzhou, China
Email: *L10045@yangtzeu.edu.cn

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Abstract

Objective: The aim of this study is to investigate how individuals with type 2 diabetes mellitus' pancreatic β-cell function index and insulin resistance index are affected by tuberculosis infection. **Methods:** The study group consisted of 89 patients with type 2 diabetes mellitus and tuberculosis infection who were admitted to Jingzhou Chest Hospital between March 2019 and March 2021. Gender and duration of diabetes were matching conditions. The control group was made up of 89 patients with type 2 diabetes who were admitted to Jingzhou Central Hospital's endocrinology department during the same period. The two patient groups provided general information such as gender, age, length of diabetes, and blood biochemical indexes such as glycosylated hemoglobin (HbA1c), fasting glucose (FPG), and fasting C-peptide (FC-P). The HOMA calculator was used to calculate the HOMA-β and the HOMA-IR, and intergroup comparisons and correlation analyses were carried out. **Results:** Regarding gender, age, disease duration, FC-P, and HbA1c, the differences between the two groups were not statistically significant ($P > 0.05$). However, BMI, FPG, HOMA-β, and HOMA-IR showed statistically significant differences ($P < 0.05$). In comparison to the control group, the study group's HOMA-β was lower and its HOMA-IR was greater. According to Spearman's correlation analysis, HOMA-β had a negative association ($P < 0.05$) with FPG, HbA1c, and the length of the disease, and a positive correlation with BMI and FC-P. A positive correlation was found between HOMA-IR and BMI, FPG, and FC-P ($P < 0.01$), as well as a correlation with the length of the disease ($P > 0.05$) and HbA1c. **Conclusions:** In type 2 diabetes mellitus combined with tuberculosis infection, the patients had higher FPG levels and lower FC-P levels, the secretory function of pancreatic β-cells was more severely impaired, and insulin resistance was more obvious.

Keywords

Tuberculosis Infection, Type 2 Diabetes Mellitus, Pancreatic β-Cell Function, Insulin Resistance

1. Introduction

Diabetes mellitus (DM) is a group of metabolic diseases characterized by chronic hyperglycemia caused by multiple etiologies. According to the International Diabetes Federation (international diabetes federation, IDF), the number of people with diabetes worldwide has increased from 463 million in 2019 to 537 million in 2021. According to the IDF, the number of people with diabetes worldwide will reach 783 million in 2045. The vast majority of them are type 2 diabetes mellitus (T2DM) [1]. The main pathophysiological features of type 2 diabetes are insulin resistance and pancreatic β-cell dysfunction [2]. And pancreatic β-cell dysfunction is present throughout the development of T2DM [3] and plays a central role in the disease process [4].

Tuberculosis (TB) is a chronic infectious disease caused by Mycobacterium tuberculosis (Mtb). According to the World Health Organization (WHO), there is a significant decrease of about 18% in reported TB infections globally in 2020 compared to 2019, of which about 90% of TB infections are in adults [5].

In this study, by comparing and analyzing the relationship between T2DM combined with tuberculosis infection and T2DM patients alone in terms of Homeostasis model assessment-β (HOMA-β) of pancreatic β-cell function index (HOMA-β) and Homeostasis model assessment-insulin resistance (HOMA-IR) [6], aiming to provide a reference basis for timely and effective glycemic control, early protection of pancreatic β-cell function, and delaying the progression of TB in clinical practice.

2. Methods

2.1. Study Subjects

In this study, 89 patients with T2DM combined with tuberculosis infection admitted and hospitalized in the First People's Hospital of Jingzhou City from March 2019 to March 2022 were selected as the study group, and the retrospective study method of 1:1 matching was used with gender and duration of diabetes mellitus as the matching conditions, while 89 patients with T2DM admitted and hospitalized in the Department of Endocrinology of the Central Hospital of Jingzhou City during the same period were selected as the control group. There were 72 males and 17 females in each of the two groups, of which the patients in the study group were 25 - 87 years old with a mean age of (58.54 ± 11.52) years, and the patients in the control group were 36-85 years old with a mean age of (59.65 ± 10.88) years.

2.2. Inclusion and Exclusion Criteria

Inclusion criteria: 1) Diagnosis of diabetes mellitus [7]: meet the diagnostic criteria of the 2020 Chinese guidelines for the prevention and treatment of type 2 diabetes mellitus: diabetic symptoms + fasting blood glucose ≥ 7.0 mmol/L (or random blood glucose ≥ 11.1 mmol/L, or 2-h blood glucose ≥ 11.1 mmol/L after glucose load). Fasting status was defined as the absence of any caloric intake for at least 8h. 2) Diagnosis of tuberculosis [8]: tuberculosis infection was diagnosed according to the health industry standard of the People's Republic of China "WS 288-2017 Diagnosis of Tuberculosis Infection" published by China in 2017. 3) Age ≥ 18 years.

Exclusion criteria: 1) Other types of diabetes mellitus. 2) Acute complications of diabetes mellitus such as diabetic ketoacidosis, diabetic hyperosmolar coma. 3) Combined with severe infectious diseases, combined with malignant tumors and other consumptive diseases. 4) Severe hepatic and renal impairment, anemia, acute cardiovascular and cerebrovascular events. 5) Recent use of glucocorticoids and other influences on blood glucose fluctuations. 6) Age < 18 years.

2.3. Research Methodology

A retrospective case-control study method with 1:1 matching ratio was used. General data such as gender, age, duration of diabetes mellitus, etc. were collected from all enrolled patients, and height and weight were routinely measured and body mass index (BMI, BMI = body weight/height^2 (kg/m^2)) was calculated. Blood samples were collected within 24 h of admission. Peptide (FC-P) concentration by electrochemiluminescence; HOMA-beta and HOMA-IR were calculated using HOMA calculator [6].

(Height and weight measurement: The subject takes off his shoes and cap, stands with his back against the wall, his heels, hips and shoulders in a straight line and touches the wall, his feet are flat on the ground, his toes are separated, his heels are together, his eyes are looking straight ahead, the upper edge of the pinna and the lower edge of the orbit are connected to form a horizontal plane, and the measurer marks the reading (in cm) on the side. When weight is measured, subjects are asked to remove their shoes and hats, remove items from their clothing pockets, and wear only simple underwear or a single piece of clothing. The subject is to stand on a calibrated weighing pan with his body straight, arms in a natural position, and eyes at eye level. When the pointer stops moving, a reading in kg is recorded.

Collection of blood samples: The subjects were instructed to fast for more than 8 hours, and peripheral venous blood was drawn on an empty stomach in the early morning of the next day to test the following indicators: FPG: glucose oxidase method; FC-P: electrochemiluminescence; HbA1c: High Speed Liquid Chromatography.)

2.4. Statistical Analysis

This study used SPSS 26. 0 software for data analysis. Measurement information

was expressed as x ± s if it conformed to normal distribution, and t test was used for comparison between groups; if it conformed to skewed distribution, it was expressed as median (quartile) [M (Q1, Q3)], and Mann-Whitney rank sum test was used for comparison between groups. Count data were expressed as frequency (constitutive ratio, n%), and comparisons between groups were performed using the χ^2 test. Correlation analysis was performed using Spearman. Differences were considered statistically significant at $P < 0.05$.

3. Results

3.1. General Baseline Characteristics of the Two Groups of Patients

There was no statistically significant difference between the two groups of patients in terms of gender, age, duration of disease, and HbA1c ($P > 0.05$). The BMI of the patients in the study group was [21.11 (19.05, 24.37)] kg /m^2, and the BMI of the patients in the control group was [25.31 (22.03, 27.41)] kg /m^2, and the difference between the two groups was statistically significant ($P < 0.05$) [Table 1].

3.2. Distribution of Patients in Both Groups across Age, Disease Duration and BMI

The age of the patients in both groups was more than 49 years old, and most of them were concentrated in the age stage of 49 - 58 years old, among which, about 41.57% of the patients in this age stage in the study group and about 30.34% in the control group. The BMI of the patients in the two groups was mainly concentrated in the range of 18.5 - 29.9 kg/m^2, of which the BMI of the patients in the study group was concentrated in the range of 18.5 - 23.9 kg /m^2, accounting for about 53.93%, and the BMI of the patients in the control group was concentrated in the range of 24 - 29.9 kg /m^2, accounting for about 58.43% [Table 2].

3.3. Comparison of FPG, FC-P, HOMA-β, and HOMA-IR between the Two Groups of Patients

Comparison of FPG, HOMA-β, and HOMA-IR levels between the two groups showed statistically significant differences ($P < 0.05$). Comparing the levels of FC-P and HbA1c in the two groups, the difference was not statistically significant ($P > 0.05$). Among them, the FPG and HOMA-IR levels of the study group were higher than those of the control group, and the HOMA-β level was lower than that of the control group [Table 3].

3.4. Multiple Linear Regression Analysis of HOMA-β and HOMA-IR in Two Groups of Patients

Multiple linear regression analysis showed that BMI, FPG, FC-P, and HbA1c levels were the influencing factors of HOMA-β ($P < 0.05$). FPG and FC-P levels were the influencing factors of HOMA-IR ($P < 0.05$) [Table 4].

Table 1. Baseline characteristics of patients in both groups.

Characteristics	Research group (n = 89)	Control group (n = 89)	Statistics	P values
Sex			0.000	1.000
Male	72 (80.90)	17 (19.10)		
Female	72 (80.90)	17 (19.10)		
Age (years)	58.54 ± 11.52	60.04 ± 10.77	−0.901	0.369
Duration of diabetes (years)	3.00 (0.71, 7.00)	3.00 (0.75, 7.00)	−0.063	0.950
HbA1c (%)	8.50 (7.10, 10.60)	8.12 (7.08, 9.82)	−1.095	0.273
BMI (kg/m^2)	21.11 (19.05, 24.37)	25.31 (22.03, 27.41)	−6.173	<0.001

Data are presented as n (%), mean ± standard deviation, or medium (Q1, Q3). HbA1c: Glycated hemoglobin; BMI: Body mass index.

Table 2. Distribution of patients in the two groups at different ages, course of disease and BMI.

Variables	Research group (n = 89)	Control group (n = 89)	Total (n = 178)
Age group (years)			
18~	1 (1.12)	0 (0.00)	1 (0.56)
29~	1 (1.12)	2 (2.25)	3 (1.68)
39~	11 (12.36)	10 (11.24)	21 (11.80)
49~	37 (41.57)	27 (30.34)	64 (35.96)
59~	20 (22.47)	29 (32.58)	49 (27.53)
69~	19 (21.35)	21 (23.60)	40 (22.47)
Duration of diabetes group (ages)			
≤1	32 (35.96)	32 (35.96)	64 (35.96)
>1, ≤5	29 (32.58)	28 (31.46)	57 (32.02)
>5, ≤15	24 (26.97)	25 (28.09)	49 (27.53)
>15	4 (4.49)	4 (4.49)	8 (4.49)
BMI group (kg/m^2)			
<18.5	17 (19.10)	1 (1.12)	18 (10.11)
18.5 - 23.9	48 (53.93)	33 (37.08)	81 (45.51)
24 - 29.9	23 (25.84)	52 (58.43)	75 (42.13)
>30	1 (1.12)	3 (3.37)	4 (2.25)

Data outside parentheses are the number of cases, and data in parentheses are rates (%).

Table 3. Comparison of FPG, FC-P, HOMA-β and HOMA-IR between the two groups [M (Q1, Q3)].

Variables	Research group (n = 89)	Control group (n = 89)	Statistics	P values
FPG (mmol/L)	8.02 (6.45, 10.91)	6.63 (5.67, 8.47)	−3.366	0.001
FC-P (ng/ml)	1.65 (1.26, 2.49)	1.73 (1.19, 2.13)	−0.873	0.383
HbA1c (%)	8.50 (7.10, 10.60)	8.12 (7.08, 9.82)	−1.095	0.273
HOMA-β	43.70 (24.95, 76.55)	60.10 (44.45, 88.55)	−2.647	0.008
HOMA-IR	1.51 (1.08, 2.21)	1.35 (0.96, 1.83)	−2.063	0.039

FPG: Fasting glucose; FC-P: Fasting C-peptide; HbA1c: Glycosylated hemoglobin; HOMA-β: The index of pancreatic β-cell function; HOMA-IR: The index of insulin resistance.

Table 4. Multiple linear regression analysis of HOMA-β and HOMA-IR between the two groups.

Variables	Standard errors	Bias regression coefficient (standardized)	T values	*P* values
HOMA-β				
FPG	0.527	−0.681	−14.615	<0.001
FC-P	1.992	0.432	10.156	<0.001
HbA1c	0.824	−0.093	−2.051	0.042
BMI	0.430	−0.084	−2.099	0.037
HOMA-IR				
FPG	0.005	0.424	18.440	<0.001
FC-P	0.020	0.883	43.022	<0.001
HbA1c	0.008	0.021	0.939	0.349
BMI	0.004	0.011	0.537	0.592

HOMA-β: The index of pancreatic β-cell function; HOMA-IR: The index of insulin resistance; FPG: Fasting glucose: FC-P: Fasting C-peptide; HbA1: Glycosylated hemoglobin; BMI: Body mass index.

3.5. Relevance Analysis

As shown by Spearman correlation analysis, HOMA-β was positively correlated with BMI and FC-P, and negatively correlated with disease duration, FPG, and HbA1c ($P < 0.05$). HOMA-IR was positively correlated with BMI, FPG, and FC-P ($P < 0.05$), and had no correlation with disease duration and HbA1c ($P > 0.05$) [Table 5].

4. Discussion

T2DM is a common chronic disease in clinic, and its main pathological mechanism is that the function of pancreatic β-cells is impaired, and the degree of impairment increases with the progression of the disease, and long-term pancreatic β-cell dysfunction can further cause insulin resistance. Tuberculosis is a common chronic disease threatening human health caused by Mycobacterium tuberculosis infection, which mainly affects the glucose metabolism of diabetic patients and aggravates the condition; at the same time, fever and other toxic symptoms caused by tuberculosis infection can lead to impaired pancreatic islet β-cell function, which reduces the function of insulin receptor and affects the secretion function of pancreatic islets [9].

Related studies have shown that gender and duration of diabetes are risk factors for PTB combined with T2DM [10] [11], and that men and long duration of disease are at higher risk of developing TB and diabetes. Therefore, this study excluded the effect of gender and disease duration, (in order to avoid the influence of the difference between the two groups of gender and the course of diabetes on the relationship between the disease and the factors, so as to more truly reflect the relationship between the research factors and the disease, therefore,

Table 5. Correlation between indexes and HOMA-β and HOMA-IR.

Variables	HOMA-β		HOMA-IR	
	r_s	P *Values*	r_s	P *Values*
Duration of diabetes	−0.241	0.001	−0.115	0.125
BMI	0.174	0.020	0.182	0.015
FC-P	0.370	<0.001	0.928	<0.001
FPG	−0.893	<0.001	0.347	<0.001
HbA1c	−0.574	<0.001	−0.001	0.986

BMI: Body mass index; FPG: Fasting glucose; FC-P: Fasting C-peptide; HbA1c: Glycosylated hemoglobin; Rs: Correlation coefficient.

this study adopted a 1:1 matching method according to gender and the course of diabetes, which can not only control the influence of confounding factors, but also improve the efficiency of the study and ensure the comparability between the study group and the control group.) but age and BMI were still influential factors. T2DM combined with tuberculosis infection as well as simple T2DM patients are more common in middle-aged and elderly people, which is consistent with the findings of this paper. It may be due to the poorer nutritional status, low immune function, and decreased ability of the body to resist infection in the elderly, which makes them a high prevalence of PTB and T2DM. In addition, the results of this study showed that the body mass index of patients in the study group was mostly in the low-normal range, while the body mass index of patients in the control group was mostly in the overweight and obese range, which is consistent with the findings of Lu *et al.* [12]. Another cohort study including 63,257 participants found that diabetes mellitus and lower BMI levels were independent risk factors for active TB, with patients with low BMI and diabetes mellitus having a risk of developing TB that was 8.3 times higher than that of obese individuals without diabetes mellitus [13]. However, it is well known that both overweight and obesity are risk factors for diabetes mellitus, and obesity not only aggravates insulin resistance in diabetic patients, but also increases the difficulty of glycemic control, as well as increasing the risk of hypertension, dyslipidemia, and cardiovascular and cerebrovascular events. Therefore, for patients with diabetes mellitus combined with tuberculosis infection, they should try to control their body weight within the normal range in order to reduce insulin resistance and decrease or delay the development of related complications.

HbA1c is the product of continuous, slow, irreversible non-enzymatic reaction between hemoglobin and glucose in erythrocytes, and its long half-life can accurately reflect the level of patients' glycemic control in the last 2-3 months, and can also be used as an important indicator for predicting chronic complications. And HbA1c level is positively correlated with the body's blood glucose level, which is of great significance in the diagnosis of T2DM, the assessment of the condition and the development of treatment programs [14]. However, the results of Li [15] showed that there was a significant difference in HOMA2-IR in

patients with different HbA1c levels, and it is still unclear as to whether HbA1c has an effect on HOMA-IR, which still needs to be confirmed by large-scale studies.

We used HOMA-β and HOMA-IR to evaluate pancreatic β-cell function. (Impaired β cell function is recognized as the cornerstone of diabetes pathophysiology. At present, the function evaluation indexes of pancreatic β cells include the function index of pancreatic β cells evaluated by the homeostatic model (HOMA-β) and the insulin resistance index (HOMA-IR) evaluated by the homeostatic model. HOMA-β and HOMA-IR are evaluation indices based on fasting blood glucose and insulin or C-peptide calculations, which can better evaluate the function of pancreatic islet β cells and insulin sensitivity. C-peptide is a substance secreted from pancreatic islet β cells in the same molecular weight form as insulin, which has the characteristics of slow metabolic clearance and is not affected by exogenous insulin, and is often used in clinical practice to assess pancreatic islet function instead of insulin [16].) The results of this study showed that the levels of FPG and HbA1c were higher in the study group than in the control group, HOMA-β was lower than in the control group, and HOMA-IR was higher than in the control group. Previous studies have found that one of the most important influences of tuberculosis infection on T2DM patients is that it induces stress hyperglycemia, and at the same time, overproduction of blood glucose can cause an acute stress response, which, through a variety of signaling pathways, comes to promote processes such as cellular proliferation and regulates insulin secretion and insulin tolerance, which in turn leads to fluctuations or worsening of blood glucose levels in patients [17] [18]. This is consistent with the findings of this paper that T2DM patients with combined tuberculosis infection had higher levels of FPG and HbA1c, indicating poorer control of patients' recent glucose levels. The results of this study showed that the FPG and HbAc levels of the patients in the study group were higher than those of the control group, HOMA-β was lower than that of the control group, and HOMA-IR was higher than that of the control group. Analyzing the reason may be that, after combining tuberculosis infection, the body releases increased inflammatory factors such as interleukin-6 (IL-6), interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α) as well as elevated levels of hormones such as dopamine and norepinephrine, which leads to increased hepatic glucose isomerism and peripheral insulin resistance, which in turn causes fluctuation and deterioration of blood glucose [19]. This indicates that in patients with combined tuberculosis infection, the higher the blood glucose level, the more serious the damage to the patient's β-cell function; the greater the magnitude of blood glucose fluctuation, the worse the patient's β-cell function. However, the mechanism of the influence of tuberculosis infection on pancreatic β-cell function is still in the exploratory stage and needs further research.

In this study, HOMA-β was found to be positively correlated with BMI and FC-P, and negatively correlated with FPG and HbA1c after correlation analysis; HOMA-IR was positively correlated with BMI, FC-P, and FPG, and not corre-

lated with HbA1c. Interestingly, the study by He Yinhui *et al.* showed that HbA1c was negatively correlated with both HOMA-β and HOMA-IR (P = 0.000). However, in this paper, HOMA-IR was shown to be positively correlated with FC-P by correlation analysis, but HOMA-IR was shown to be negatively correlated with FC-P by descriptive analysis of data from both groups of patients. According to the results of the study, serum FC-P levels were lower in patients with combined tuberculosis infection, suggesting that there may be insufficient pancreatic β-cell secretion. The reasons for this may be, firstly, the insidious onset of tuberculosis and the long course of the disease is gradual, due to long-term chronic infection caused by pancreatic islet inflammation, resulting in damage to pancreatic β-cells pancreatic islet cell secretion disorders; secondly, tuberculosis, especially tuberculosis to a certain degree of the development of the condition of the lungs will be irreversible damage, which affects the function of the lungs, and when the organism of the long-term hypoxia combined with chronic depletion of the nutritional deficiency, there will be multi-organ function impairment, and the lung function will be affected by the chronic consumption. Third, during tuberculosis infection, the toxic reaction of tuberculin and fever and other toxic symptoms can affect the secretion function of pancreatic β-cells, leading to a decrease in the body's sensitivity to insulin and the emergence of insulin resistance [20] [21]. In this case, further research is needed to analyze whether the insufficient secretion of pancreatic β-cells is due to the temporary inhibition of pancreatic β-cell function by glycolipotoxicity and acute stress after infection with Mycobacterium tuberculosis, or whether the pancreatic β-cells function decreases due to the progression of the disease.

In summary, when T2DM is combined with tuberculosis infection, which is more common in middle-aged and elderly patients, patients have higher FPG levels and lower FC-P levels, the secretory function of pancreatic β-cells is more severely impaired, and insulin resistance is more obvious. However, further studies are needed to confirm whether the impaired β-cell secretory function in combined TB infection is due to temporary inhibition of glycolipotoxicity after infection or due to disease progression. For patients with T2DM combined with tuberculosis infection, pancreatic β-cell function should be assessed at an early stage to formulate a targeted treatment program to slow down disease progression and improve prognosis.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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