Glycemic Control, Serum Leptin and Lipid Profile in Patients With Pulmonary Tuberculosis: Effect of Initial Two Months Anti-Tuberculosis Therapy

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الخلاصة

الاهداف: لتقييم تاثيرات التدرن الرئوي على علامات السيطرة السكرية (مستوى سكر الدم، الببتيد-ج، مستوى الانسولين ومقاومة الانسولين) مستوى اللبتين وصورة الدهون (الكوليسترول، الدهون الثلاثية، الكوليسترول في الدهون الواطئة الكثافة، الكوليسترول في الدهون العالية الكثافة ومؤشر تصلب الشرايين) وتقييم تاثيرات العلاج المكثف لمدة شهرين بالادوية المضادة للتدرن على مستوى هذه المفردات بالمقارنة مع مجموعة الضبط من الاصحاء.

الطرق: ادخل لهذه الدراسه 43 مريضاً بالتدرن الرئوي الفعال، محالين من العيادة الاستشارية للامراض الصدرية والتنفسية في الموصل (العراق) مع اربعين من الاصحاء من اعمار واجناس مقاربة لمجموعة المرضى كمجموعة ضبط. تم تحديد مستوى الكلوكوز، السببتايد، الانسولين واللبتين مع مفردات صورة دهون الدم، وتحديد مقاومة الانسولين بمعادلة خاصة بعد شهرين من العلاج المكثف لمجموعة المرضى (الايزونيازايد 75 ملغم والريفامبسين 150 ملغم والبايرازين امايد 400 ملغم وايثامبيوتول 275 ملغم) يومية اربع حبات من المركب المذكور مع جرعة يومية واحدة من فيتامين بي 6 10 ملغم. تم اعادة قياس لبعض المفردات المذكورة اعلاه. تم حساب دلالة كتلة الجسم للمرضى ومجموعة الضبط باستخدام معادله خاصه.

النتائج: لم يكن هنالك اختلافاً معنوياً في مفردات السيطرة السكرية ومستوى اللبتين ومفردات صورة الدهون في الدم بين مجموعة مرضى التدرن الرئوي الحاد قبل العلاج ومجموعة الضبط.

بعد شهرين من العلاج كانت هنالك زيادة معنوية في دلالة كتلة الجسم، مستوى اللبتين ومستوى الدهون الثلاثية في مرضى التدرن الرئوي بالمقارنة مع فترة ما قبل العلاج.

الخلاصة: لم يؤثر مرض التدرن الرئوي الحاد (قبل العلاج) تاثيراً معنوياً على مفردات السيطرة السكرية، مستوى اللبتين، ومفردات صورة الدهون. اما العلاج المركز للشهرين الاوليين فقد أثر تأثيرا معنويا على دلالة كتلة الجسم، مستوى اللبتين ومستوى الدهون الثلاثية في مرضى التدرن الرئوي بينما لم يكن له تاثير معنوي على مفردات السيطرة السكرية وبقية مفردات صورة دهون الدم.

مفتاح الكلمات: التدرن الرئوي، السيطره السكريه، مستوى اللبتين في مصل الدم، صورة الدهون.

Abstract

Objectives: To evaluate the effect of pulmonary tuberculosis (TB) on glycemic control (fasting serum glucose "FSG", serum insulin, C-peptide and insulin resistance), serum leptin and lipid profile (total cholesterol 'Tc', triglyceride "TG", low density lipoprotein cholesterol "LDL-C", high density lipoprotein cholesterol "HDL-C" and atherogenic index AI) and to evaluate the effects of intensive 2-months anti-tuberculosis therapy on these parameters in comparison to healthy controls.

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Methods: Forty three patients with active pulmonary tuberculosis from the Advisory Clinic for Chest and Pulmonary Diseases in Mosul City were included in this study, with 40 apparently healthy age and sex matched subjects as controls. Assessment of serum concentration of FSG, C-peptide, serum insulin levels and insulin resistance, with serum leptin and lipid profile were done for the patients and controls. After two months with intensive anti-TB therapy (isoniozid "INH" 75 mg, rifampicin 150mg, pyrazinamide 400mg and ethambutol 275mg) 4 tablets as a single dose in the morning with vitamin B_6 10mg daily, the same parameters were reassessed for the patients. Body mass index were calculated for both the patients and control using especial equation.

Results: With the exception of body mass index (BMI), there was insignificant differences with regard the parameters of glycemic control, serum leptin and parameters of lipid profile between newly diagnosed patients with pulmonary TB in the pre-therapy stage and healthy controls.

After 2 months of therapy, there was a significant increase in BMI, serum leptin and serum TG with insignificant differences in the other parameters under study.

Conclusion: In this study active pulmonary TB as a disease did not affect parameters that represent glycemic controls, serum leptin and lipid profile. Intensive 2-months therapy with anti-TB drugs brings about a significant increase in BMI, serum leptin and TG with insignificant effect on glycemic control, and other parameters of lipid profile.

Key words: Pulmonary Tuberculosis; glycemic control, serum leptin level; lipid profile.

Introduction

Tuberculosis (TB) remain a major cause of morbidity and mortality worldwide, especially in Asia and Africa. Under the surveillance and results of the survey conducted by the World Health Organization (WHO) in 2006, the number of TB causes worldwide is estimated to be 9.2 million , accounting for 1.7 million deaths[1]. The success of the treatment depends on the use of appropriate anti-TB drugs, the adherence of the patient to treatment, the sensitivity of myobacteria to drugs, and the control of associated diseases[2] . TB often leads to severe weight loss, probably through the production of inflammatory mediators[3]. Wasting, in turn, affects the inflammatory response, suppresses cellular immunity, and aggravates the outcome of TB[4]. In these complex relations between TB, nutritional status and the host immune response, leptin is a possible mediator[5]. Borderline diabetes mellitus (DM) has been reported with TB causes [6] and DM has been considered a risk factor for TB[7]. Takayasu et al[8] observed that rifampicin induced an early phase hyperglycemia which he attributed to augmented intestinal absorption. An

over dose of isoniazid (INH) may cause hyperglycemia[9], while in rare circumstances diabetes may become difficult to control in patients on pyrazinamide[10]. With regard lipid profile in patients with pulmonary TB, Guzman et al[11] and Perez-Guzman[12] found that most patients with pulmonary TB had low total cholesterol levels and that values of about 90mg/dl were strongly associated with mortality in those patients with miliary disease. The aims of this study was to assess body Mass Index (BMI), serum glucose, insulin, C-peptide, insulin resistance, serum leptin and lipid profile in newly diagnosed causes with active pulmonary TB and to assess the effect of intensive 2 months therapy with anti-TB drugs on these parameters in comparison to healthy controls.

Patients and Methods

Patients included in this study, which was conducted from December 2011 to May 2012, were obtained from Advisory Clinic For Chest and Respiratory Diseases in Mosul City, Iraq. The analytical work was done in the Department of Pharmacology, College of Medicine, at the University of Mosul. Approval to conduct this study was obtained from Ethical Committees of the main Health Centre in Ninevah, Mosul City and the College of Medicine- University of Mosul.

Eligibility for entry into the study included typical symptoms of pulmonary TB: fibrocavitary lung infiltrate on chest radiograph and at least one sputum specimen staining positive with Ziehl-Neelsen for acid-fast bacilli. All patients included in this study were non or ex-smoker and had no history of drug usage (including vitamins). Additional criteria for females included neither being pregnant nor lactating. Also excluded from this study, seriously ill-patients, patients with miliary TB and patients with renal , hepatic or metabolic problems.

Out of 50 patients interviewed and examined, only 47 fulfilled the criteria for this study and only 43completed the follow-up study. After diagnosis, patients with pulmonary TB were treated according to the standard protocol at the Advisory Clinic (patients gives 4 tablets of Rimstar®, a fixed dose-tablet containing 4 anti-TB drugs INH 75mg ,rifampicin 150mg, pyrazinamide 400mg, ethambutol 275mg) with vitamin B_6 tablet 10mg daily to be swallowed before breakfast for the initial 2 months. Approximately 10ml of venous blood was drawn using disposable plastic syringes from patients with pulmonary TB prior to initiation of therapy and by the end of the two months intensive therapy. The sera were separated after centrifugation of the blood and kept frozen at (-20)C^o pending analysis. Only estimation of the FSG was immediately done.

Forty apparently healthy volunteers (12 females, 31 males, age range from 18-62 years), with mean age ± standard deviation (SD) of 40.37 ± 11.64

years and a mean± SD BMI of 21.08 ± 1.55, with no previous history of TB were recruited as controls to establish the normal values for FSG, C-peptide, serum insulin, serum leptin, lipid profile and insulin resistance by calculation. Serum glucose was measured by oxidase-peroxidase colorimetric method (Lotta and Turner,1975) [13] by using a kit supplied from Biocon (Germany). Serum C-peptide was measured by enzyme-linked immuno solvent assay (ELISA) technique, using the DRG C-peptide ELISA kit(Germany). Serum insulin was measured by ELISA technique using a kit from GenWay Bio Tech Inc.(USA). Seum leptin level was measured using ELISA technique with IBL leptin ELISA kit (Germany). Serum total cholesterol (Tc), high density lipoprotein cholesterol (HDL-C) and triglyceride (TG) concentration were measured by enzymatic method using kits supplied by Biolabo Company (France).

Calculation of low-density lipoprotein cholesterol concentration (LDL-C) was done according to the following equation:

LDL-C = TC – (HDL-C) –TG /2.2mmol/L Friedewaldet et al, 1972[14]
Atherogenic index (AI) was calculated using the following equation
AI= TC/HDL-c [15]

Insulin resistance was calculated using the following equations:

$$\textbf{Insulin resistance} = \frac{\textbf{fasting blood sugar x serum insulin}}{\textbf{22.5}}$$ [16]

Body Mass Index (BMI) were calculated using the following equations:
BMI = weight (Kg) / height (m^2) [17]

Statistical analysis

The data of the study, subjected to statistical analysis were expressed as mean ± Standard Deviation (SD). Statistical comparisons were performed using paired and unpaired t-test. A P-value < 0.05 was considered to be statistically significant.

Results

The characteristic of the patients and controls were shown in table (1). With regard glycemic control in patients with pulmonary TB (before starting therapy), there was insignificant differences in the mean values of FSG, serum insulin , C-peptide and insulin resistance in comparison with healthy controls (Table 2). There was also insignificant differences with regard serum leptin, TC, TG, LDL-c, HDL-c and AI (Table 3).

There was insignificant differences in the parameters of glycemic controls in patients with pulmonary TB (after 2 months therapy) with a significant differences in the mean serum level of leptin and TG in comparison to pre-therapy stage (Tables 4,5).

Table (1):The characteristics of T.B. patients and control group.

Groups	Parameters	Mean ± SD		*P*- Value	
Control	Age (Year)	**40.43 ± 13.10**		**0.98****	
T.B. patients	Age (Year)	**40.37 ± 11.64**			
Control	BMI (Kg/m^2)	**22.30 ± 1.80**		**0.002***	
T.B. patients	BMI (Kg/m^2)	**21.08 ± 1.55**			
		Control		**T.B. patients**	
		No.	**%**	**No.**	**%**
Sex	Male	28	70.0	31	72
	Female	12	30.0	12	28
	Total	40	100	43	100
	***P*- Value**	**0.84****			

* Significant difference from control at p≤0.01
** Non Significant difference from control at p≤0.01

Table (2): Comparison of parameters of glycemic control between control group & patients with pulmonary TB (before therapy).

Parameters	Mean ± SD		*P*- value
	Control (n=40)	Before (n=43)	
FSG (mg/dL)	93.3±8.83	95.00±11.77	0.46 *
Serum Insulin (µU/ml)	4.41±2.66	4.61±2.90	0.74 *
C-Peptide (ng/ml)	4.20±2.10	3.95±2.17	0.60 *
Insulin Resistance	1.01±0.63	1.07±0.67	0.70 *

* Non- significant difference from control using unpaired t-test

Table (3): Comparison of Serum leptin & lipid profile between control group and patients with pulmonary T.B (before therapy).

Parameters	**Mean ± SD**		***P*- value**
	Control (n=40)	**Before (n=43)**	
Serum leptin (ng/ml)	6.11±2.60	7.23±3.33	0.10 *
TC (mmol/l)	4.10±0.56	4.08±0.38	0.86 *
TG (mmol/l)	1.23±0.27	1.20±0.20	0.61 *
LDL-c (mmol/l)	2.18±0.63	2.20±0.42	0.87 *
HDL-c (mmol/l)	1.40±0.22	1.34±.23	0.30*
AI	3.03±0.62	3.10±0.49	0.61*

* Non- significant difference from control using unpaired t-test.

Table (4): Comparison of glycemic control in patients with pulmonary T.B in the pre and post-therapy stages.

Parameters	Groups	Mean ± SD	*p*-value
FSG (mg/dL)	Before	95.00±11.77	0.92 (NS)
	After	94.76±11.10	
Serum Insulin (µU/ml)	Before	4.61±2.90	0.64 (NS)
	After	4.70±2.93	
C-Peptide (ng/ml)	Before	3.95±2.17	0.56 (NS)
	After	4.10±2.10	
Insulin Resistance	Before	1.07±0.67	0.52 (NS)
	After	1.09±0.72	

NS= Non- significant using paired t-test.

Table (5): Comparison of Serum leptin& lipid profile in T.B. patient group & (before & after) therapy.

Parameters	Groups	Mean ± SD	*p*-value
Serum leptin(ng/ml)	Before	7.23±3.33	0.001*
	After	7.94±3.45	
TC (mmol/l)	Before	4.08±0.38	0.23(NS)
	After	4.09±0.36	
TG (mmol/l)	Before	1.20±0.20	0.008*
	After	1.23±0.21	
LDL-c (mmol/l)	Before	2.20±0.42	0.15(NS)
	After	2.21±0.38	
HDL-c (mmol/l)	Before	1.34±.23	0.06(NS)
	After	1.32±.21	
AI	Before	3.10±0.49	0.132(NS)
	After	3.14±0.43	

* Significant difference using paired t-test
NS= Non- significant

Discussion

This study revealed no significant differences in the parameters of glycemic controls (FSG, serum level of insulin, C-peptide and insulin resistance) in patients with active pulmonary TB (before therapy) in comparison to healthy controls. After 2 months of intensive chemotherapy with anti-TB drugs, no differences were observed with regard the parameters mention above.

Few studies with regard the subject have been done. In the early part of this century the prevailing view, as suggested by Rost[18] was that TB patient do not develop DM with any greater frequency than the non-TB. Newly this view has been changed, it has been reported that a diabetic-like state is present in TB patients[19]. On the other hand impaired glucose tolerance secondary to TB has also been reported[20].

A Nigerian study[21] done on 54 patients with active pulmonary TB reported that 3 patients had oral glucose tolerance tests values in the diabetic range and 20 had impaired glucose tolerance. The only published study with regard the some measured parameters as in this study, is that conducted by Karachunski et al., (1995)[22], studying the function of the pancreatic incretory apparatus in patients with active pulmonary TB by analyzing the blood levels of insulin, C-peptide and glucose before and after glucagon stimulation. They reported a pronounced enhancement of insulin secretion and at the same time signs of relative insulin deficiency appeared as persistent hyperglycemic and apparently delayed concentration peaks of insulin and C-peptide.

After anti-TB therapy, Takayasu et al[8] observed that rifampicin induced an early phase hyperglycemia which he attributed to augmented intestinal absorption. Other anti-TB drugs interfere very rarely with blood sugar level. An overdose of INH[9] may cause hyperglycemia.

In this study serum leptin level was not significantly different in patient with pulmonary TB (before therapy) and the controls and significantly increased after 2 months of intensive anti-TB therapy in comparison to pre-therapy stage.

In human, circulating Leptin levels are increased in obesity and are regulated by fasting, feeding and body weight changes [23,24] .In addition to playing a role in energy regulation, leptin also regulates endocrine and immune functions [25] . In some reports, leptin levels are low in TB [26], though other earlier studies have shown conflicting results [27,28].

Low leptin levels were observed in patients with large infiltrates even after adjustment for BMI[26].

our finding with regard no significant differences in leptin levels between patients with pulmonary TB in the pre-therapy stage and the healthy controls, may be explained by the fact that serious cases and patients with miliary TB were excluded from the study.

After starting treatment, leptin levels were slightly elevated, but remained low during the treatment period [26,29] ,the mechanism remains unknown.

Tuberculosis leads to severe weight loss, probably through the production of inflammatory mediators [3]. Wasting, in turn, affects the inflammatory response, suppresses cellular immunity and aggravates the outcome of TB [4]. In these complex relations between TB, nutritional status and the host immune response, leptin is a possible mediator[5].

With regard lipid profile, no significant differences in the parameters of lipid profile (TC, TG, LDL-c, HDL-c and AI) in patients with active pulmonary TB (before therapy) in comparison to healthy controls. After 2 months of intensive anti-TB therapy, there were only a significant increase in serum TG levels in such patients in comparison to pre-therapy stage.

Rashtchizadeh and Valankhah (2006)[30] in agreement with our studied lipid profiles and lipoprotein (A) levels in patients with pulmonary TB, no marked differences between serum levels of TC, TG, LDL-c and HDL-c were reported in such patients in comparison to healthy controls. In a recent study conducted by Metwally and Raheem (2012) [31], they reported hypocholesterolemia in Egyptian patients with pulmonary TB at the time of diagnosis and they concluded that it is a consequence of the disease rather than a risk factor as serum cholesterol significantly increased in such patients after treatment.

This might be the first follow-up study in patients with active pulmonary TB concerning glycemic control(FSG, serum C-peptide and insulin levels, insulin resistance), serum leptin and lipid profile before and after intensive 2-months antiTB therapy.

In conclusion: serum leptin, lipid profile and glycemic control does not affected by tuberculosis in this study and anti-TB intensive 2 months therapy bring about significant changes in BMI, serum leptin and TG in such patients.

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