Oxidant/Antioxidant Status, C-reactive Protein and Serum Leptin in Patients with Pulmonary Tuberculosis: Effect of Vitamin E Supplemention

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الخلاصة

لتقييم تاثيرات التدرن الرئوي على علامات جهد الاكسدة المالونديليهايد، وحالة مضادات الاكسدة الكلية وتوتين التفاعلي عالي الحساسية ومستوى اللبتين في مصل الدم ومقارنة تاثيرات العلاج المكثف لمدة شهرين بالادويه المضاده للتدرن مع العلاج المكثف لمدة شهرين بالادويه المضاده للتدرن مع فيتامين أي على مستوى هذه المفردات.

تم اختيار مرضى التدرن الرئوي الفعال، من العيادة الاستشارية للامراض الصدرية والتنفسية في الموصل (العراق). المجموعة الاولى مكونة من 38 مريضاً والمجموعة الثانية مكونة من 28 شخص اصحاء من اقارب المرضى كمجموعة مقارنة. تم قياس مستوى المالونديليهايد، حالة مضادات الاكسدة الكلية وتوتين التفاعلي عالي الحساسية ومستوى اللبتين لمجموعة المرضى ومجموعة الضبط. بعد شهرين من العلاج التقليدي (ايزونيازايد 75ملغم، الريفامبسين 150ملغم، بيرازين امايد 400ملغم والايثامبيوتول 275ملغم) يوميه اربعة حبات من المركب المذكور مع جرعة يوميه (10ملغم فيتامين داي الفا) من العلاج التقليدي المذكور اعلاه مع فيتامين أي بجرعة 400وحدة دولية وتم اعادة قياس المفردات المذكورة اعلاه حسب دلالة كتلة الجسم باستخدام معادله خاصه.

بعد شهرين من العلاج التقليدي او العلاج التقليدي مع فيتامين أي كان هنالك انخفاض معنوياً في مستوى المالونديليهايد والبروتين التفاعلي عالي الحساسية نوع ج وارتفاع معنوياً في مستوى حالة مضادات الاكسدة الكلية والبتين ودلالة كتلة الجسم في مرضى التدرن الرئوي بالمقارنة مع فترة ما قبل العلاج ونسبة التغيير منحرفة باتجاه التاثير الايجابي لاضافة فيتامين أي.

التدرن الرئوي الحاد يصاحبه ارتفاع في جهد الاكسدة وارتفاع في مستوى البروتين التفاعلي عالي الحساسية نوع ج والعلاج التقليدي او العلاج التقليدي مع فيتامين أي سبب تحسن معنوياً في جهد الاكسدة وتثبيط الاستجابة الالتهابية مع توجه باتجاه التاثير الايجابي لاضافة فيتامين أي.

مفتاح الكلمات التدرن الرئوي, جهد الاكسدة, المالونديليهايد, مضادات الاكسدة الكليه, البروتين التفاعلي نوع –ج, العلاج التقليدي, فيتامين اي.

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Abstract

Objectives: To evaluate the effects of pulmonary Tuberculosis (TB) on markers of oxidative stress (malondialdehyde "MDA" and total antioxidant status "TAS"), high sensitivity C-reactive protein (hs-CRP) and serum leptin and to compare the effects of standard intensive 2 months anti-TB therapy with the standard intensive anti-TB therapy plus vitamin E supplementation on the parameters.

Methods: Two group of patients with active pulmonary TB from the Advisory Clinic for Chest and Respiratory Diseases in Mosul City were included in this study.Group one consistent of 38 patients and group two consistent of 28 patients, with forty healthy age and sex matched subjects as controls. Assessment of concentrations of MDA, TAS, hs-CRP and leptin were done for both patients and controls. After two months with either the traditional intensive therapy (isoniazid "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 or , the intensive traditional therapy plus vitamin E 400 IU/day as a supplementation therapy, the same parameters were reassessed for the patients. Body mass index(BMI) were calculated by using special equation.

Results: After 2 months of either the traditional therapy or the traditional therapy plus vitamin E ,there was a significant reduction in MDA and hs-CRP with significant increase in TAS ,leptin serum levels and BMI in patients with pulmonary TB in comparison to pre-therapy stage and the percentage of variation shifted towards the beneficial effect of vitamin E add- on therapy group.

Conclusion: Active pulmonary TB associated with oxidative stress and an increase in the levels of hs-CRP and both traditional therapy or the traditional therapy plus vitamin E resulted in a significant improvement in oxidative stress and cause suppression of inflammatory responses with the beneficial effects shifted towards the add-on of vitamin E as a supplementation therapy.

Keywords: Pulmonary tuberculosis, oxidative stress, malondialdehyde, total antioxidant status, C-reactive protein, traditional therapy, vitamin E.

Introduction

Tuberculosis (TB) is a major cause of death around the world , with most of the 1.5 million deaths per year attributed to the disease occurring in developing countries[1]. One of the most important and common complaints in TB patients is weight loss. Antimicrobial treatment after increases weight but TB patients may remain under-weight even six months after the successful chemotherapy[2]. Leptin, the product of the "ob" gene, regulates food intake and energy expenditure. In humans circulating leptin levels are increased in obesity and arte regulated by fasting, feeding and body weight changes[3]. It has been suggested that leptin mediates anorexia in chronic inflammatory states[4]. The relationship between leptin and pulmonary TB is not completely understood. There were very few studies relating the level of leptin and tumor necrosis factor-α before and after anti-TB therapy and their results are contradictory[4,5]. Mycobacteria are capable of inducing reactive oxygen species (ROS) production by activating both mononuclear and polymorphnuclear phagocytes that may posses antimicrobial activity. The enhanced level of free radical production, although designed to combat the invader, has the potential to damage the host; however, host tissue damage is limited by the concurrent enhancement of the antioxidant defenses of the host[6]. In TB patients, there are also some reports of poor antioxidant defense that may expose to oxidative host tissue damage[7,8]. Vitamin E level is lower in patients with pulmonary TB[8] .C-reactive protein (CRP), an acute phase protein has been reported to be significantly elevated in patients with active pulmonary TB, normalizing over time on therapy, thereby correlating with clinical response[9,10]. The physiological roles of CRP are numerous, one of the critical function being its importance in host defense[11]. The aim of this study was to assess serum leptin, malondialdehyde (MDA) , total antioxidant status (TAS) and CRP in patients with active pulmonary TB and to assess the effects of traditional intensive 2 month therapy or the traditional intensive therapy plus vitamin E on these parameters.

Patients and Methods

Patients included in this study, which was undertaken from December 2011 to June 2012, were obtained from Advisory Clinic for Chest and Respiratory Diseases in Mosul City, Iraq. The analytical work

was performed in the Department of Pharmacology, College of Medicine, at the University of Mosul. Approval was obtained from ethical committees of the main health center 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 not included in the study seriously ill-patients, patients with miliary TB and patients with renal , hepatic or metabolic problems.

Out of 72 patients interviewed and examined, only 68 fulfilled the criteria for this study and only 66 completed the follow-up study. Patients were randomly divided into two groups: one receiving the traditional intensive 2-months therapy and the second receiving the traditional intensive 2-months therapy plus vitamin E 400 I.U/day capsule.

After diagnosis, patients with pulmonary TB were treated either with the standard protocol at the Advisory Clinic. Patients were given 4 tablets of Rimstar ®, a fixed close tablet containing 4 anti-TB drugs(Isoniazid (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, or this standard therapy plus vitamin E capsule 400I.U/d for two months. Approximately 10ml of venous blood was drawn using disposable plastic syringes from both groups of TB patients 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.

Forty apparently healthy volunteers (30 males and 10 females) age ranged from 18 to 60 years with a mean 35.87 ± 11.03 years with no previous history of TB were recruited as controls to establish the normal values for MDA, TAS, hs-CRP and serum leptin.

Serum MDA levels were established using a thiobarbituric acid (TBA) assay[12], TAS were assayed according to the method described by Miller et al [13] using Randox TAS Kit (Randox Laboratories Ltd, UK). hs-CRP was measured using enzyme-linked immunosorbent assay (ELISA) for quantitative determination of hs-CRP in human sera (Cummings, 2001)[14] using Biochek hs-CRP ELISA kit (Foster city-

USA). Serum leptin level was measured using the IBL leptin ELISA kit (Germany). Body mass index (BMI) was calculated according to the following equation:

BMI = Weight (Kg) / Height (m^2) [15]

Statistical analysis:

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

Results

There was a significant differences in the mean values of BMI, MDA, TAS and hs-CRP between patient with pulmonary TB (in both groups)before therapy and the controls with insignificant differences in the mean serum level of leptin (Table 1).

There was a significant increase in BMI, serum TAS and leptin levels, with significant reduction in serum MDA and hs-CRP in patients with pulmonary TB after either standard therapy or the standard therapy plus vitamin E in comparison to pre-therapy stages (Table 2,3).

Table 4 showed the percentage of variation in the measured parameters after either the standard therapy or the standard therapy plus vitamin E. From the percentage of variation in the measured parameters between patients receiving the anti-TB alone and those receiving anti-TB plus vitamin E supplementation, one can reach the judgment that its more beneficial to add vitamin E to the standard anti-TB therapy with regard reduction in MDA, CRP and the raise in TAS.

Table 1: Comparison of patients with pulmonary TB before therapy and the controls with regard the measured parameters.

Parameter	Group	Min	Max	Mean ± SD	95% CI of mean	P value
BMI	Before traditional therapy	18.01	21.10	20.83 ± 1.58	20.31 – 21.35	<0.0001
	Before traditional therapy+VitaminE	18.20	23.20	20.57 ± 1.51	19.98 – 21.15	
	control	19.30	25.10	22.32 ± 1.57	21.82 – 22.83	
hs-CRP mg/L	Before traditional therapy	1.48	2.30	1.82 ± 0.20	1.76 – 1.89	
	Before traditional therapy+VitaminE	1.50	2.35	1.84 – 0.20	1.76 -1.92	<0.0001
	control	0.24	0.70	0.46 – 0.11	0.42 – 0.49	
MDA µmol/L	Before traditional therapy	1.60	2.80	2.01 – 0.26	1.92- 2.09	
	Before traditional therapy+VitaminE	1.60	2.60	1.98 – 0.26	1.87 -2.08	<0.0001
	control	0.50	1.10	0.81 – 0.15	0.75 – 0.86	
TAS mmol/L	Before traditional therapy	0.80	1.40	1.14 – 0.15	1.09 – 1.19	<0.0001
	Before traditional therapy+VitaminE	0.80	1.40	1.10 – 0.15	1.04 – 1.16	
	control	1.50	2.10	1.81 – 0.17	1.76 – 1.87	
Leptin ng/ml	Before traditional therapy	0.83	15.20	6.61 – 3.18	5.56 – 7.65	<0.0001
	Before traditional therapy+VitaminE	0.89	17.10	6.14 – 3.51	4.77 – 7.50	
	control	0.90	11.10	6.21 – 2.57	5.83 – 7.03	

Table 2.Comparison of measured parameters between patients with pulmonary TB before and after traditional therapy plus vitamin E.

Parameter	Group	Mean ± SD	Mean differences± SD	95% CI of mean	P-value
BMI	Before traditional therapy +Vitamin E	20.57± 1.51	-0.75±0.45	-0.93- -0.58	<0.0001
	After traditional therapy +Vitamin E	21.33± 1.43			
hs-CRP mg/L	Before traditional therapy +Vitamin E	1.84±0.20	0.55±0.14	0.49-0.61	<0.0001
	After traditional therapy +Vitamin E	1.28±0.14			
MDAµmol/L	Before traditional therapy +Vitamin E	1.98±0.26	0.68±0.16	0.62-0.75	<0.0001
	After traditional therapy+VitaminE	1.29±0.17			
TAS(mmol/l)	Before traditional therapy +Vitamin E	1.10±0.15	-0.73±0.12	-0.78- -0.68	<0.0001
	After traditional therapy +Vitamin E	1.83±0.16			
Leptin(ng/ml)	Before traditional therapy +Vitamin E	6.14±3.51	-0.90±0.62	-1.15- -0.66	<0.0001
	After traditional therapy + Vitamin E	7.05±3.65			

Table 3.Comparison of measured parameters between patients with pulmonary TB before and after traditional therapy.

Parameter	Group	Mean ± SD	Mean differences± SD	95% CI of mean	P-value
BMI	Before traditional therapy	20.83± 1.58	-0.66±0.71	-0.89- -0.43	<0.0001
	After traditional therapy	21.50± 1.45			
hs-CRP mg/L	Before traditional therapy	1.82±0.20	0.47±0.18	0.41-0.53	<0.0001
	After traditional therapy	1.35±0.16			
MDAµmol/L	Before traditional therapy	2.01±0.26	0.38±0.13	0.34-0.43	<0.0001
	After traditional therapy	1.62±0.24			

TAS mmol/L	Before traditional therapy	1.14±0.15	-0.13±0.11	-0.17- -0.09	<0.0001
	After traditional therapy	1.27±0.10			
Leptin ng/ml	Before traditional therapy	6.61±3.18	-0.69±1.07	-1.04- -0.34	<0.0001
	After traditional therapy	7.30±3.10			

Table 4. Percentage of variation in response in the measured parameters after either traditional therapy or the traditional therapy plus vitamin E.

Parameters	Anti-TB +Vitamin E Mean differences ±SD	Anti-TB alone Mean differences ±SD	P-value
BMI	0.75±0.45	0.66± 0.71	0.5
hs-CRP mg/L	-0.55±0.14	-0.47±0.18	0.06
MDA µmol/L	-0.68±0.16	-0.38±0.13	<0.0001
TAS mmol/L	0.73±0.12	0.13±0.11	<0.0001
Leptin ng/ml	0.90±0.62	0.69±1.07	0.3

Discussion

This study showed a significantly lower BMI, TAS and a significantly higher hs-CRP and MDA with insignificant difference in serum leptin levels between patients with pulmonary TB in the pre-therapy stage and the controls, and after either traditional intensive 2 month therapy or the intensive 2 months therapy plus vitamin E , there was a significant increase in BMI, TAS and serum leptin with a significant reduction in serum MDA and hs-CRP in such patients in comparison to pre-therapy stages.

Wiid et al., (2004)[16], reported that active TB patients showed a significantly lower TAS compared with controls and that TAS values increases during therapy. Dhia and Thanoon (2010) [17] also concluded that active pulmonary TB is associated with oxidative stress (as reflected by the increased serum level of MDA and reduced serum level of TAS) and the increase in CRP indicated pulmonary TB is associated with an inflammatory response.

In an attempt to kill mycobacteria, host cells generate huge amounts of ROS [18]. One of the manifestation of these ROS is lipid peroxidation. These high levels of ROS are often cytotoxic and may cause host tissue damage, such as lung fibrosis and lung dysfunction in patients with pulmonary TB if antioxidant defenses of the host are deficient[19].In the present study TAS was measured instead of determining individual antioxidant enzymes and molecules, low levels of TAS were observed in patients with pulmonary TB. This might be due to malnutrition or exhaustion in an attempt to neutralize the heavy load of free radicals in these patients. In fact, the combination of malnutrition (leading to decreased supplementation of antioxidants) and

enhancement of ROS generation may represent a pathogenic loop that results in markedly enhanced oxidative stress during TB infection [20,21]. This study also showed that the hs-CRP levels in patients with pulmonary TB were significantly higher than those of healthy controls and that the administration of both standard anti-TB or standard anti – TB plus vitamin E for 2 months was associated with a significant reduction in its level. CRP has been reported to be significantly elevated in patients with active pulmonary TB, normalizing over weeks on therapy, thereby correlating with clinical response [9,10]. Higher CRP have also been associated with more sever TB and poor diagnosis [22]. mycobacterium TB and its components have been shown to stimulate mononuclear phagocytes in vitro to release interleukine-6 (IL-6), which are regarded as inflammatory mediators , IL-6 is known to induce hepatic acute phase reactants (including CRP). Several clinical and laboratory findings support the relation between IL-6 and CRP[23].

Conflicting data have been reported for leptin levels during infection. Elevated Leptin levels were reported in studies conducted by Çakir et al [24] and Yuksel et al[25]. On the other hand Van Crevel et al [26] have reported that plasma leptin and ex vivo Interferon – (IFN-gamma) production were low and increased with successful anti-TB therapy.

After vitamin E as an add-on therapy , in this study there was a significant reduction in MDA , hs-CRP with a significant increase in TAS and leptin in patients with pulmonary TB.

Mohod and Kumar., 2012 [27] in agreement with our study results, concluded that patients with pulmonary TB were unable to produce sufficient amounts of antioxidants to cope up with the increased oxidative stress and that antioxidants supplementation along with anti-TB therapy may prove beneficial and may help in fast recovery in the management of such cases

Seyedrezazadeh et al., (2008) [28] reported a significant reduction in MDA levels with a significant increase in TAS levels in patients with pulmonary TB receiving vitamin E and selenium as supplementation in comparison to those receiving only the anti-TB therapy. Vitamin E supplementation has been shown to improve T-cell mediated immune functions[29], also vitamin E is the most important lipid-soluble antioxidant and an integral component of all lipid membranes that serves to protect lipid membrane from attack by ROS[21].

The only published study with regard effects of vitamin E supplementation on the levels of CRP, reported by Devaraj and Jialal .,

(2000)[30].They concluded that α-tocopherol supplementation significantly lowered levels of CRP and monocyte interleukin-6 in normal volunteers and type 2 diabetic patients.

Only one study with regard the effects of vitamin E intervention and leptin level in rat, conducted by Shen et al., (2010)[31] .They reported that vitamin E intervention increased the expression of both leptin and adiponectin, and association analysis showed that serum leptin levels correlated positively with body fat mass. They concluded that although vitamin E is well known for its antioxidant properties, it could potentially affect adipocytokine levels through a non-antioxidant mechanism, including inhibition of protein kinase C and regulation of cell growth and CD36 expression [32, 33].

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