Immune boosting role of vitamin E against pulmonary tuberculosis

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Abstract: Tuberculosis is one of the leading causes of mortality in Pakistan which is linked with malnutrition and weak immunity. Such people are more prone to chronic infections including TB. The current study aimed to assess the effect of supplementation of Vitamin E on the immune status of human subjects against pulmonary tuberculosis. A total of 80 patients with pulmonary TB were divided into treatment group (vitamin E) and control group (Anti-tuberculosis regime). Presence of acid fast bacilli in sputum sample, Erythrocyte sedimentation rate, total leucocytes counts, body mass index and mid arm muscle circumference (MAMC) were recorded as per standard protocol. Levels of vitamin E, IgG, IgM and T-Cell count were determined before and after treatment. The results showed that 16% males and 33% females were underweight who consumed 1145 kcal energy instead of 2270 kcal per day and 19.5 gram protein instead of 78.6 grams. A non significant effect of vitamin E on ESR and TLC values was observed but significant increase in level of immunoglobulins (IgG, IgM) and T-cell types ($CD4^+$ and $CD8^+$) was observed in patients as compared to control group. Results indicate that vitamin E plays important role in enhancing immunity of patients against TB.

Keywords: Tuberculosis, malnutrition, vitamin E, BMI, MAMC.

INTRODUCTION

Tuberculosis (TB) is an infectious bacterial disease caused by *Mycobacterium tuberculosis* (MTB) which is prevailing from 3000-5000 years BC (Zink *et al*., 2003). As per WHO TB is a global health emergency and is one of the leading causes of unavoidable deaths in young adults (Kumar and Clark, 2001). It has been estimated that about 33% of the world's population is at risk of TB. It was thought that TB is the disease of third world country but from last decade prevalence of TB in developed countries is also increased. Number of positive cases of TB in population of South East Asia is up to 44%. Pakistan is graded at fifth position among 22 high graded countries (Saira *et al*., 2013).

In TB patients, there is continuous decline in levels of macro- and micro-nutrients which badly affects their muscle and immune response. Patients in hospitals require urgent dietary support along with the recommended treatment (Saleem *et al*., 2012). Deficiency of various micronutrients is causing secondary immunodeficiency and predominate the individuals for infections related morbidity. The individuals are more prone to tuberculosis. Vitamin E increases the intracellular killing capacity of cells by protecting lipid membranes with decrease requirement of glutathione peroxidase and by reducing leakage of free radicals into the cytosol (Miller *et al*., 2000). It has been observed that during the course of the disease, the demand for various nutrients also increases to maintain homeostasis and tissue repair, so supplementation of food additives increase the success rate of TB therapy. Use of micronutrients along with therapeutic agents also improves outcome of the disease (vanLettow *et al*., 2004).

Studies showed that patients with pulmonary tuberculosis have lower vitamin E level than normal person. Vitamin E and Selenium plays an important role, as micronutrients, in improving health quality and immunomodulation during the course of the disease. In body, vitamin E works with selenoprotein and glutathione peroxidase and blocks the production of free radicals and ultimately the damaging process by these radicals is blocked (Seyedrezazadeh *et al*., 2006). Dietary counseling is one of the effective tools to control malnutrition/wasting associated with tuberculosis. In Pakistan there are no proper dietary protocols for TB patients, they often have poor nutritional status. Therefore, this study is designed to assess whether dietary counseling would increase nutrient intake and improve nutritional status in patients with tuberculosis.

Although vitamin E has an anti-oxidative and immunomodulatory function, it is not known whether vitamin E supplements given together with anti-tuberculosis drugs would increase the efficacy of the anti-tuberculosis treatment or not. Thus, we decided to conduct this double-blind, placebo controlled trial to investigate the effects of vitamin E supplementation on the clinical, microbiological and roentgenological outcomes of patients with pulmonary tuberculosis.

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MATERIALS AND METHODS

Ethical consideration

Ethical approval was obtained from an ethical review committee of the University of Veterinary and Animal Sciences, Lahore and Services Institute of Medical Sciences (SIMS), Lahore. Verbal and written consent was obtained from each participant. The laboratory findings of the study participant were communicated with the responsible clinician assigned at TB clinic.

Selection of patients

In order to observe effect of Vitamin E supplementation as immune-booster in pulmonary tuberculosis patients, patients registered in SIMS, Lahore were selected. An inclusion criterion in current study was patients with age groups from 20-40, with clear signs of pulmonary tuberculosis. They were confirmed for having positive acid-fast bacilli in their sputum samples. Those patients with other forms of tuberculosis or being on treatment for more than two months were excluded from the study.

History and Clinical evaluation of the patients

Initial diagnosis of pulmonary tuberculosis was based on the basis of history of evening pyrexia, productive cough, hemoptysis, malaise, tiredness, anorexia, chest pain, clinical examination by an expert pulmonologist, assessment of the presence of B.C.G scar, response to tuberculin skin test and chest x-ray (CXR) with or without cavity lesions (WHO, 2000).

Anthropometric measurements

a. Body Mass Index (BMI)

The parameters of anthropometric measurements which were used include weight in (kg) and height in (feet). BMI was calculated as weight in kg/height in meter square= (kg/m^2) (Mahan and Escott-Stump, 2004). The calculated BMI of each patient was compared with standard BMI reference table for Asians (WHO, 2004).

Table 1: Symptoms of tuberculosis along with and their frequency

Symptoms	Frequency
Productive cough	78 (97%)
Hemoptysis	07 (9%)
Malaise	39 (48%)
Tiredness	36 45(%)
Anorexia	52 (65%)
Chest pain	47 (59%)
Night sweating	39(48%)
Fever	77 (96%)
Presence of BCG Scar	80(100%)

b. Mid Arm Muscle Circumference (MAMC)

Mid arm muscle circumference (MAMC) and triceps skin-fold muscle (TSF) were also measured. MAMC was measured by taking measurement of Acromion process and olecranon process of ulna by using measuring tape. The reading was divided by 2 to mark mid arm area. MAC was taken by rounding measurement in cm at mid-point of arm. TSF was taken by measuring the skin fold thickness from mid-arm in mm. MAMC was calculated through following formula:

$$\text{MAMC for female patients} = \frac{\left[\text{MAC cm} - (\pi \times \text{TSF cm})\right]^2 - 6.5}{4x\pi}$$

$$\text{MAMC for male patients} = \frac{\left[\text{MAC cm} - (\pi \times \text{TSF cm})\right]^2 - 10}{4x\pi}$$

MAMC was used to assess total body muscle and protein energy malnutrition PEM (Gibson, 2005).

Dietary Data

a. 24 –hour recall

Three days 24 hour dietary recall was used to assess the protein and energy intake of patients. The recall involved details of subject's food and fluid consumed by the subjects. Mean of 3 day 24 hour recalls was taken an average dietary intake record. 24 hour recall is generally accepted and authenticated method by USDA (Gibson, 2005).

b. Food frequency questionnaire

A food frequency questionnaire (FFQ) checklist was generated and used to assess food and beverage intake. This was done by interviewing the subjects. FFQ was then used to assess the food habits of patients. It is a reflective review of specific food intake (Dwyer *et al*., 2003). The mean energy and protein was compared with standard recommended dietary allowances (RDA) for calories and protein.

Study design

In this study a total of 80 patients (n=50 male, n=30 female) of pulmonary tuberculosis were selected during the period from February to October 2016. They were divided into treatment group (Vitamin E and anti-tuberculosis drug) and control group (anti-tuberculosis drug) comprising forty patients per group. Both groups were treated with anti tuberculosis regimen (Combination of Ethambutol at the dose rate of 15mg/kg, Rifampicin at the dose rate of 10mg/kg, Isoniazid at the dose rate of 5mg/kg and pyrazinamide at the dose rate of 25mg/kg) as recommended by (WHO, 1999). Control group received anti-tuberculosis regimen and placebo (Starch capsule). Treatment received anti-tuberculosis regimen with Vitamin E (100 mg per day). Information regarding age, gender, location of residence, source of income/economic status, dietary status and habit of smoking/drugs abuse was also recorded. During the study period, patients were advised to visit the hospital every alternate week to collect anti-TB drugs and vitamin E capsules (where applicable).

Clinical evaluations

In order to determine the response of the treatment on patients, chest X-rays were performed after two and six months of the therapy. The patients having cavitary lesion(s) in lungs, the decrease in radius of the cavity were noted. Microbiological examinations of sputum sample for the presence of MTB was done after every 15 days during two months of the treatment and were tested through ZN staining techniques (Monica, 2006). Results were recorded for conversion of acid-fast positive bacilli to acid-fast negative bacilli (*Mycobacterium tuberculosis*) indicating treatment response. Treatment was continued for 6-8 months as recommended by WHO (1999).

Microbiological, Hematological and Biochemical parameters

Blood sample from the patients were collected through venepuncture and various microbiological, hematological and biochemical tests were performed including ESR and TLC (Monica, 2006). Determination of IgG and IgM level against *Mycobacterium tuberculosis* using commercially available ELISA kit (IBL International, GmBH), and determination of CD4+ and CD8+ count in patient's blood through Flow Cytometery. The $CD4^+$ and $CD8^+$ cells were counted using Becton-Dickinson fluorescence activated cell sorter (FACS) Calibur using Cell Quest software as per instructions mentioned in the manual (Mehta *et al*., 2011). Level of Vitamin E was measured through HPLC (Castle *et al*., 1985).

STATISTICAL ANALYSIS

Comparison between groups (before and after treatment) was made using 2-tailed t-test. Impact of micronutrient supplementation on cell mediated immunity was evaluated through correlation. *P*-value less than 0.05 were considered significant (Douglas, 2000).

RESULTS

The results of history and clinical evaluation of the patients showed that most of TB patients (97%) were having cough for the last three weeks, about 96% of the subjects were having high fever at night time and other symptoms observed were hemoptysis, malaise, tiredness, anorexia, chest pain and night sweating with the relative frequency at the rate of 9%, 48%, 45%, 65%, 59% and 48% respectively (table 1). Out of 50 male subjects 82% were falling in normal BMI range whereas only 2% were overweight and 16% were underweight. The data of female patients (n=30) showed that 60% patients had a normal BMI, 7% were overweight and 33% were underweight (table 2). Results of male patients showed that 32% have wasted, 34% depleted and 28% marginal MAMC values. Only 3 patients were with adequate muscle mass. Among females majority of subjects were having depleted muscle mass showing 27% wasted, 36% depleted and 30% with marginal muscle mass (table 3).

Results of dietary recall (table 4) showed that on an average 19 grams of protein was consumed by patients, whereas 78.6 grams protein was the actual requirement based on calculations. The dietary intake recall (table 5) during 3 days of the enrolled subjects revealed that the frequency of eating bread and cereals, meat, milk and milk products, fruits and vegetables was 98%, 93%, 90%, 95% and 70% respectively. Results showed that 100 % of patients consumed chapatti as a staple food. Most of the patients (70%) never consumed rice or consumed once a week while 30% of the patients consumed rice twice a week. White bread was consumed by the patients (62.5%) daily in their breakfast while 24% consumed it twice a week and 13.7% patients never consumed it at all. The data showed there was no trend of consumption of bran bread. 48.7% of subjects consumed biscuits almost daily (7 days a week), 45% do not consumed biscuits at all and 6.3% consumed biscuits once or twice a week. 72.5% patients did not consume rusk even once a week. Mutton consumption was minimal with 95% do not consuming even once a week. Beef was also not consumed by most of patients (92%) who do not consumed beef at all. Similarly not a single patient consumed fish during study period. The results showed that egg was consumed by most of the patients (83.7%) daily and 16.2% consuming twice a week. 81.2% of the patients consumed chicken twice a week. Legumes were consumed by 83.75% of patients twice a week. Likewise, milk and yoghurt was not consumed by 91.2% of patients. Butter consumption was not found even once a week by 100% of patients during study period. Fruit consumption was minimal with 95% do not consuming even once a week. Vegetables were noted to be 50% almost daily and 50% twice a week. Fats were consumed by 100% of patients more than once a day in any form. Sweets consumption was minimal with 88.7% do not consuming sweets or sweet dishes at all. There was a declined trend in consumption of fried foods with 87% do not eat fried foods even once a week. Bakery products were consumed by 7.5% more than once a day and 90% do not consume at all. Tea consumption was recorded to be twice a week (72.5%). Ready to eat foods was not taken by 100% of patients during study time.

Microbiological evaluation revealed that 20% of the individuals were positive with AFB load while 62% of the individuals were negative with AFB load. Among the positive AFB individuals scanty, one plus, two plus and three plus patients were 20%, 25%, 20% and 35% respectively (table 6). Average ESR in the control and treatment group was approximately the same during study period (table 7).

In start the average of TLC in both groups was high but after treatment the treatment group has less total leucocytes count (TLC) than control group. The Means and standard deviations of TLC are depicted in (table 8). The level of vitamin E in treatment group has remarkably

Table 2: BMI of the study individuals

Body Mass Index (BMI) n=80				
Gender	Male (n=50)		Female (n=30)	
Ranges	%	Frequency (f)	%	Frequency (f)
Underweight	16	8	33	10
Normal	82	41	60	18
Overweight	2	1	7	2
Obese	0	0	0	0

Table 3: Mid arm muscle circumference (MAMC)

Mid arm muscle circumference (MAMC) (cm)										
Gender	Wasted		Depleted		Marginal		Adequate		Total	
	f	%	f	%	f	%	F	%	f	%
Male	16	32	17	34	14	28	3	6	50	62
Female	8	27	11	36	9	30	2	7	30	38
Total	24	29	28	35	23	29	5	7	n=80	

f = Frequency

Table 4: Comparison of protein consumed with required (gm)

Comparison of protein(gm) required with consumed			
Variable	Group	Mean	Sig
Protein n=80	Consumed	19.5	0.000
	Required	78.6	

*p-value<0.005

Table 5: Food Frequency Questionnaire (FFQ)

Food Frequency Questionnaire (FFQ)								
Food	<1/week		1-2 days / week		3-7days / week		>1/day	
	f	%	f	%	f	%	f	%
Chapatti	0	0	0	0	0	0	80	100
Rice	58	70	22	30	0	0	0	0
White bread	11	13.7	19	24	50	62.5	0	0
Bran bread	80	100	0	0	0	0	0	0
Biscuits	36	45	5	6.3	39	48.7	0	0
Rusk	58	72.5	14	17.5	8	10	0	0
Table salt	80	100	0	0	0	0	0	0
Mutton	76	95	4	5	0	0	0	0
Beef	74	92	6	8	0	0	0	0
Fish	80	100	0	0	0	0	0	0
Egg	0	0	13	16.2	67	83.7	0	0
Chicken	2	2.5	65	81.2	13	16.2	0	0
Legumes	0	0	67	83.75	13	16.25	0	0
Milk	80	100	0	0	0	0	0	0
Milk in any foam	80	100	0	0	0	0	0	0
Milk shakes	80	100	0	0	0	0	0	0
Yoghurt	73	91.2	2	2.5	5	6.2	0	0
Butter	80	100	0	0	0	0	0	0
Fruits	76	95	4	5	0	0	0	0
Vegetables	0	0	40	50	40	50	0	0
Fats	0	0	0	0	0	0	80	100
Sweets	71	88.7	19	11.3	0	0	0	0
Fried items	70	87	10	13	0	0	0	0
Bakery products	72	90	1	1.2	1	1.2	6	7.5
Tea	0	0	58	72.5	0	0	22	27.5
Ready to Eat food	80	100	0	0	0	0	0	0

Table 6: Sputum samples for AFB load

Specimen for AFB stain	Positive	Negative
Sputum (n= 70) 87.5%	20 (25%)	50 (62%)
	Scanty 04(20%)	
	One plus 05 (25%)	
	Two plus 04 (20%)	
	Three plus 07 (35%)	
Non Sputum (n=10) 12.5%	20 (25%)	50 (67%)

Table 7: Comparison of Mean value of ESR in different groups at various durations

Group	Mean mm/hr. Start	Mean mm/hr. 2nd Month	Mean mm/hr. 4th Month	Mean mm/hr. 6th Month
Control	54.55	11.25	11.25	10.75
Treatment	50.55	11.9	11.9	9.55

Table 8: Comparison of Mean value of TLC in groups at various durations of treatment

Group	Mean cells / mm^3 start of the treatment	Mean cells / mm^3 2nd Month	Mean cells / mm^3 4th Month	Mean cells / mm^3 6th Month
Control	11570	9310	8900	8560
Treatment	11825	9520	8740	8390

Table 9: Level of Vitamin E in the blood before and after treatment

Level of vitamin E in the blood Before Treatment			Level of vitamin E in the blood after Treatment	
Group	Mean	Standard Deviation	Mean	Standard Deviation
Control	3.64	1.14	4.41	3.74
Treatment	3.65	1.22	24.58	5.96

Table 10: Level of IgG in the blood before and after treatment

Level of IgG in the blood before treatment			Level of IgG in the blood after treatment		
Group	Mean	Standard Deviation	Group	Mean	Standard Deviation
Control	596.8	117.72	Control	626.85	131.05
Treatment	595.47	121.65	Treatment	1188.421	98.24

Table 11: Level of IgM in the blood before and after treatment

Level of IgM Before Treatment			Level of IgM after Treatment		
Group	Mean	Standard Deviation	Group	Mean	Standard Deviation
Control	26.3	5.69	Control	28.7	7.30
Treatment	19.26	10.89	Treatment	182.73	11.51

Table 12: CD4 cell count before and after treatment

CD4 Cell count before treatment			CD4 Cell count after treatment		
Group	Mean	Standard Deviation	Group	Mean	Standard Deviation
Control	399.15	43.77	Control	418.55	63.90
Treatment	394	48.42	Treatment	1153.684	65.02

Table 13: CD8 cell count before and after treatment

CD8 cell count before treatment			CD8 cell count after treatment		
Group	Mean	Standard Deviation	Group	Mean	Standard Deviation
Control	116.25	25.36	Control	124.1	28.40
Treatment	116.26	24.84	Treatment	677	49.66

been increased in the blood after giving vitamin E to the patients. However there was no increase in the level of vitamin E in blood of control group patients after treatment (table 9). The mean values of level of IgG and IgM in blood of treatment groups have significantly increased than control group (table 10 & 11).The mean value of level of $CD4^+$ and $CD8^+$ cells in blood of treatment group has significantly increased than control group (table 12 & 13).

DISCUSSION

The results of current study showed that most of the patients including male and female were having low economic status and it seems that most of poor people suffer with TB as they have deprived immune status and cannot eat balanced diet or they eat diet without proper minerals and vitamins. The common clinical presentation of pulmonary TB (PTB) include, coughing more than two weeks, fever, night sweats, hemoptysis and wasting (Campbell and Bah-Sow, 2006). The health status of an individual is an important determinant for the risk of progression to TB disease. The incidence of malnutrition in TB has been reported and various researches have been conducted to assess nutritional status in different countries. Malnutrition has also been associated with increasing susceptibility to TB. Studies have shown TB patients suffer from wasting and micronutrient deficiency (vanLettow *et al*., 2004). A study conducted in USA on the relationship between malnutrition and tuberculosis showed that nutritional support of undernourished populations, who are at high risk of TB, may reduce the incidence of TB in such groups (Murray *et al*., 1990)[9]. Concurrent macro and micronutrient deficiency compromises the immune system function which in turn increases the risk of TB reactivation (Macallan *et al*., 1998). Various mechanisms like, poor dietary intake due to loss of appetite, poor absorption of nutrients from the intestine and increase uptake of nutrients by specific target tissue due to increase body metabolism, were associated with nutritional deficiency in TB patients (Mathur, 2007).

Since anti-TB treatment was given to malnourished TB patients, there is a possibility that nutritional deficiency may impair treatment outcomes. One past study conducted in Indonesia reported that micronutrient supplementation resulted in an earlier elimination of tubercle bacilli from the sputum (Karyadi *et al*., 2002). On the basis of our results we can say that TB patients have poor nutritional status and nutrition education sessions must be organized for the patients with poor dietary choices and minimal caloric and protein intake.

The results of present study showed that subjects with normal BMI had better response to tuberculosis treatment as compare to the subjects who were underweight. One past study conducted in Malta also suggested that there was a strong relationship between TB and BMI. The patients with low BMI index could develop TB again after recovery. The strong association between BMI and TB was only seen in pulmonary TB patients and not in extra-pulmonary TB patients and it was probably due to the reason that the patients with low BMI may be more prone for reoccurrence of TB in the lungs. An explanation of this reason may be due to the congenital apical lung bullae that effect almost 15% of the population (Casha and Scarci, 2017). A study conducted in Taipei also revealed a strong association of BMI with tuberculosis mortality in which 14.2% deaths occurred in normal weight patients, 24.4% deaths occurred in underweight patients and 10.3% deaths occurred in overweight patients (Yen *et al*., 2016). Another study also supported our results that individuals with increased BMI have improved immune response and reduction in mortality due to TB (Colleen *et al*., 2010). The good response of tuberculosis treatment in patients with normal to high BMI could be due to the fact that they have improved immune functions which could help in early recovery from the disease. Our findings showed that in Pakistan due to very low socioeconomic status and inadequate availability of food, subjects cannot eat properly leading to low BMI, due to which they might have delay in TB treatment response. Therefore, a proper nutritional counseling should be a helpful tool in treating tuberculosis.

Our findings showed that most of the patients do not have adequate muscle mass and mostly fall in the category of depleted, marginal or wasted muscle mass with low daily caloric and protein intake. A study conducted in Indonesia demonstrated that TB patients had significantly decreased BMI, skin fold thicknesses (biceps, triceps, sub-scapular, supra-iliac), MAMC, proportion of fat, and also decrease in the level of albumin, hemoglobin, vitamin A and zinc in the blood (Karyadi *et al*., 2002). The results of our study showed that due to poverty and malnutrition most TB patients fall in the category of wasting or depleted muscle mass so nutritional improvements in the TB patients may play a novel approach towards fast recovery. As by adding micronutrients including vitamin E to TB patients might be helpful to improve their wasting or depleted status toward adequate muscle mass.

The ESR and TLC of the TB patients showed that there was no significant effect of Vitamin E supplementation on ESR and TLC value of the patients and it is independent of the treatment. It is not 100% necessary of all TB patients to have high value of ESR and the justification of this reason is in line with the findings of Al Marriand Kirkpatrick, 2000 in which 33% had a normal ESR (<10 mm/hour) 67% had an elevated ESR (> or =10 mm/hour) at the time of diagnosis and there was no significant correlation between either age or size of tuberculin skin test reactivity and ESR values (Al-Marriand Kirkpatrick, 2000).

The mean value of level of vitamin E has significantly increased in the blood after giving vitamin E to the patients. However there was no increase in the level of vitamin E in blood of control group patients after treatment. The result of these findings clearly showed that due to increase level of vitamin E in the blood of patients, immunity would have been enhanced which showed better treatment outcomes. The results of our study are in line with the findings of (Seyedrezazadeh *et al*., 2006).On the basis of our findings we could conclude that subjects having increase level of vitamin E in their blood would have developed increased immunity and there would be less or no side effects of antibiotics therapy and these individuals responded early from treatment as compared to those subjects who did not received vitamin E.

The level of IgG and IgM in the blood of study patients indicated that the supplementation of micronutrients such as vitamin E increased the level of IgG and IgM in the blood of treatment group except control group. The increased level of IgG and IgM in the blood depicts more immunity due to which patients' body could resist side effects of the antibiotics. One past findings are in line with our results that zinc and vitamin A deficiency is related with a decreased production of IgA in blood due to deficiency of vitamin and micro minerals so we can say that supplementation of vitamin E and selenium enhances levels of Abs in blood which in turn enhances immunity and improves treatment outcomes against TB (Kheirouri and Alizadeh, 2014).

The increased level of $CD4^+$ and $CD8^+$ cells in the blood of study patients indicated that the supplementation of vitamin E increased the immunity and due to which patients' body could tolerate side effects of the antibiotics leading to quick recovery. Our results are in line with the findings of previous study conducted to determine the effect of supplementation of micronutrient on treatment outcome, morbidity, cell counts and mortality in pulmonary TB adults. The findings of the study indicated that micronutrients supplementation had significantly increased $CD3^+$, $CD4^+$ and $CD8^+$ cell counts (Villamor *et al*., 2008).

CONCLUSION

In light of above findings it is concluded that Vitamin E supplementation should be recommended along with anti-tuberculosis therapy for better treatment and immunity of TB patients. The emphasis of TB care unit should be made on improving nutritional status of patients to the best possible level.

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