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RESEARCH ARTICLE

The Effect of Nutritional State on Immune Response for Adults Patients with Tuberculosis

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Abstract

Malnutrition is observed frequently in patients with pulmonary tuberculosis (TB), but their nutritional status, especially of micronutrients, is still poorly documented. The objective of this study was to investigate the nutritional status of patients with active TB compared with that of healthy controls in Babylon providence. In a case-control study, 50patients aged 18–75 y with untreated active pulmonary TB was compared with 40 healthy controls. Anthropometric and micronutrient status data were collected. Compared with the controls, TB patients had significantly lower body mass index and concentrations of serum albumin, andplasma zinc and vitamin C. And studying the factors that affecting the cell mediated immunity including phagocytic index, CD56 and IFN-γ for TB patients.Blood samples were collected from patients group and control group to estimate phagocytic index, interferon gamma (IFN-γ), CD56 and Vitamin C by ELISA (Enzyme linked immunosorbent assay) method and to estimate zinc and Albumin level were also estimated by using spectrophotometer. The cell mediated parameters showing that there is a significantly decreased ($p< 0.05$) in phagocytosis activity of neutrophils in TB patients (6.04%) compared to control group (11.70%) and there is no significantly increased ($p> 0.05$) of IFN-γ level in the TB patients (0.159) IU/ml compared to control group (0.157) IU/ml .CD56 level in TB patient (78.043)IU/ml compared to control group (74.473) which was with no significantly increased ($p > 0.05$). The level of zinc in serum is significantly decreased ($p<0.05$) in the TB patients (51.18) g/dl compared with control (113.44) g/dl and albumin level in serum is a significantly increased ($p<0.05$) in the TB patients (38.973) g/dl compared with control (50.2) g/dl.

Keywords: *TB. Tuberculosis. IFN-γ. Malnutrition*

Introduction

Tuberculosis (TB) caused by *Mycobacterium tuberculosis*, stays a leading cause of morbidity and mortality globally [1]. Estimated 9.0 million cases, 5.7 million new cases and 1.5 million deaths are attributing to TB in 2013 [2]. Iraq is one of the countries with a relatively high rate for TB incidence (64/100,000).

The WHO assumed that the incidence rate of TB in Iraq is constant. Iraq has a higher incidence of TB than majority of neighboring countries. Several risk factors such as diabetes mellitus, HIV-infected individuals, and smoking, malnutrition, alcohol and hostimmunogenetic factors are associated with susceptibility to TB [3]. Mycobacterium tuberculosis infection induces both cell-mediated and humeral immune responses in an individual [4].

Infection with Mycobacterium tuberculosis results in a variety of conditions ranging from asymptomatic infection to active tuberculosis with pulmonary or extra pulmonary involvement in most cases. A variety of clinical features of TB results from cell-cell interactions that is promote by cytokines produced by immune cells during response to MT infection [5].

Various types of inflammatory cytokines of both innate and adaptive immune systems coordinate the immune response of an individual to M. tb infection [6]. On the way to prevent tissue damage, active tuberculosis was related with decrease Th1 and increase production and action of suppressing cytokines generated by Th2 cells, which act by deactivating macrophages, modulating proinflammatory cytokines, and reducing the

function of T cells for antigen presenting. TH17 have been identified as a key inflammatory cytokine involved in a number of diseases including pulmonary tuberculosis [7]. IFN-γ is the major cytokine of Th-1 cells; therefore, as proinflammatory immune response, it protects against MTB and activates macrophages for killing intracellular mycobacteria [8].

IL-10 inhibits production of IFN-γ and antigen specific T helper 1 proliferation responses, up-regulates T helper 2 responses and prevents activation of macrophage [9]. In addition, the functioning of various antigen-presenting cell types like the B lymphocytes, macrophages, dendritic cells (DCs), and Kupffer cells are decreased in malnutrition [10].

Micronutrient deficiency suppresses immunity by affecting innate, T cell mediated and adaptive antibody responses, leading to dysregulation of the balanced host response. This situation increases susceptibility to infections, with increased morbidity and mortality. In turn, infections aggravate micronutrient deficiencies by reducing nutrient intake, increasing losses, and interfering with utilization by altering metabolic pathways. Insufficient intake of micronutrients occurs in people with eating disorders, in smokers, in individuals with chronic alcohol abuse, in certain diseases, during pregnancy and lactation, and in the elderly [11].

Deficiency of vitamin C has been implicated as a risk factor for tuberculosis [12]. Vitamin C highly concentration in leukocytes and used rapidly during infection in fact it has been defined as stimulant of leukocyte function, vitamin C may also play a significant role in the regulation of the inflammatory response [13].

Zinc deficiency is known to cause impaired cell mediate immunity this can increase susceptibility to TB because the cell mediated immunity plays a major role in the disease [14]. This study aims to assess the effects of nutritional status of tuberculosis patients on immune response against tubercle bacilli.

Materials and Methods

Patients

Study population included patients with pulmonary and extra pulmonary tuberculosis the total of (50) tuberculosis patient consisting of (31) males and (19) females were involved in this study. Their age range from (18-75) years. All tuberculosis case was clinical diagnosed by a specialist clinician. Those patients were admitted to Babylon Center of Tuberculosis and Chest disease during the period November 2017-February 2018.

Control

A total of 40 apparently healthy subject (24 males and 16 females) were involved as healthy controls group. The age of controls group range was (18 to 70) years.

Diagnosis of *M. tuberculosis*

Diagnosis of *M. tuberculosis* by traditional phenotypic such as acid fast bacilli (AFB), Lowenstein-Jensen (LJ) medium technique and molecular technique by GeneXpert system.

Nutritional Factors

Albumin and Zinc are estimated by spectrophotometer according to (Bio labo-France) while the vitamin C estimated by ELISA technique according to (Elabscince-China).

Immunological Factors

INF-γ and CD56 are estimated by ELISA technique according to (Elabscince- China).

Statistical Analysis

The statistical analysis including measures of central tendency, dispersion and t-test were carried out using a commercially available software program (SPSS 21, SPSS Inc., and Chicago, Illinois, USA). P value less than 0.05 was considered statistically significant.

Ethical Approval

Ethical approval was carried out through ethical committee of medical microbiology department in collage of medicine, ethical committee in Babylon College of Medicine, ethical committee in Babylon Health Directorate, verbal and written consent from subjects involving in this work.

Results and Discussion

TB cases were diagnosed by GeneXpert all (50) TB patients were positive in GeneXpert. The mean of serum albumin levels were (38.973 g/L) for the TB patients and (50.2g/L) for the control, this indicating significant

decrease in albumin serum levels in TB patients when compared with control persons. The mean of albumin serum level for the patients (38.973g/L) is clinically normal since it remains within the normal value (34 g/L-48 g/L) Table (1).

Table 1: The Nutritional Factors in TB patients and healthy control

Nutritional Factors	TB patients(n=50) Mean±SD	Controls(n=40) Mean ± SD	Significance between Patients and Controls
Albumin	38.763 ± 1.46	52.352± 3.32	P<0.05
Zinc	51.18 ± 6.38	113.44 ± 27.73	P<0.05
Vitamin C	13.16 ± 2.77	41.87 ± 2.50	P<0.05

Following stimulus through infection or injury, the macrophage release a monokine, interleukin-1, which stimulates the hepatocyte to secrete a number of acute phase proteins, These acute phase reactants have been shown to serve a variety of functional roles during tissue repair of infection or inflammation and in several host immune defense mechanisms, CRP has been shown to cause bacterial capsular swelling, promotion of agglutination complement fixation and enhancement of phagocytosis. [16].

Since albumin may act as intracellular antioxidant; this interprets our result that serum level of albumin is decreased significantly during TB infection. The synthesis of albumin decreases relatively in malnourished persons [15]. The mean level of serum zinc was 51.18µg /dl for TB patients and 113.44 µg /dl for control subjects. This study reveals a significant difference between the serum zinc level for patients and control subjects ($p < 0.05$). It showed that zinc level was lower in TB patients than controls.

This finding was matched with other study [17, 18] that mentioned that serum zinc levels were significantly reduced in patients with pulmonary tuberculosis (PTB) compared to healthy controls. The reason for low serum zinc levels in TB could be multifactorial: Firstly a change in distribution of zinc in the body tissue is known to occur in chronic infections , with a net flow of zinc to the liver for the synthesis of acute phase reactants including metaloenzymes. Secondly, zinc may be utilized by Mycobacterium *tuberculosis* for the growth and multiplication [14]. That significant decrease in serum zinc levels of TB patients when it was compared to control group [17]. Other studies showed that Anti-tuberculosis therapy results were significantly increased in serum zinc levels during treatment [19]. While [20] showed that zinc supplementation improves the effect of tuberculosis medication after 2 months of anti-tuberculosis treatment and the results in earlier sputum smear conversion.

The mean of Vitamin C (VC) concentration in TB patients was (13.458)ng/ml, while in control groups was (41.236)ng/ml. The study significantly shows a difference between TB and controls, ($p < 0.05$).The study shows that VC is significantly lower in TB than controls. This finding was matched approximately with [12] who found that the level of VC was lower in patients Tuberculosis in comparison with healthy control.

This finding is also matched with [12] who showed that the VC can kill *M. Tuberculosis* through hydroxyl radicals generated though Fenton's reaction. Also, study of [22] showed that VC acts as a trigger for the induction of dormancy in *M. Tuberculosis*; VC induces DeveR (DosR) regulon which is responsible for the development of dormancy in bacteria. Interferon Gamma (IFN-γ) concentration in serum of TB patients was 0.159 pg/ml, while in controls was 0.157 pg/ml. From the result was found no significant difference between patients and controls when p value was ($p > 0.05$) Table (2).

Table 2: The Immunological Factors in TB patients and healthy control

Immunological Factors	TB patients(n=50) Mean ± SD	Controls(n=40) Mean ± SD	Significance between Patients and Controls
IFN-γ	0.159± 0.0051	0.157±0.003	P = 0.0341

CD56	78.043±18.361	74.473±21.116	P = 0.562
Phagocytic activity	6.04±1.973	11.7±1.471	P < 0.05

This mathematic analysis does not reflect the true difference between patients and control, no difference here means inability to respond to mycobacterial antigen. As an immunological rule intracellular bacterial infection causes induction in the immune system represented by the expression of Th-1 response that secretes cytokines mainly IFN-γ which function to stimulate the bactericidal activity of macrophage [23]. Thus no elevation in the concentration of IFN-γ in TB patients reflects inability of those hosts to respond to bacterial antigens which are considered as immunological energy [24, 25].

The CD56 concentration in serum of TB patients was 78.043µg/dl, while in controls was 74.473µg/dl.TheCD56 was used in this work as a marker for NK cells that plays a direct role in both innate and specific immunity [26]. In light of the fact that natural killer (NK) cells can produce IFN-γ [27], express cytolytic activity and respond to conserved determinants of microbial pathogens through Toll-like and other innate immune receptors [28].This study investigated whether these cells could constitute one variable in the immune response to *M. tuberculosis*. Human NK cells display extensive phenotypic heterogeneity and plasticity within and between individuals. For example, the level of CD56 surface expression discriminates NK cells whose frequencies in the blood vary significantly between individuals [29]. NK cells mediate antibody – dependent cell cytotoxicity (ADCC) and spontaneous cytotoxicity. In human ADCC is mediated by the $CD56^{dim,}$ $CD16^{+}$ NK cell subset and is triggered by CD16 engaging the Fc portion of compelled IgG on target cells [30]. The mean value of phagocytic index for TB patients and controls were (6.04%, 11.70%) respectively. It was cleared that the phagocytic index decreases significantly in TB patients.

This finding was matched with that recorded by [31] found that neutrophils isolated from the peripheral blood of tuberculosis patients reduced phagocytic activity. Also, [32] have demonstrated that neutrophils make a very significant contribution to innate immunity to TB, an activity associated with their antimicrobial peptides. Elucidation of the regulation of these peptides could lead to the development of novel strategies to prevent and treat TB. The TB patients involved in this work exhibited a significant decreasing in nutritional testes as well as immunological testes as compared to healthy controls.

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References

1. Abdalla AE, Lambert N, Duan X, Xie J (2016). Interleukin-10 Family and Tuberculosis: An Old Story Renewed. Int. J. Biol. Sci., 12(6):710-717.
2. Shaviya N, Budambula V, Webale MK, Were T (2015) Circulating Interferon-Gamma Levels Are Associated with Low Body Weight in Newly Diagnosed Kenyan Non-Substance Using Tuberculosis Individuals. Interdisciplinary Perspectives on Infectious. Diseases, 9.
3. World Health Organization (WHO) (2011) WHO report 2011. Global tuberculosis control. WHO/HTM/TB/2011.16.Geneva: WHO.
4. Maglione PJ, Xu J, Chan JB (2007) cells moderate inflammatory progression and enhance bacterial containment upon pulmonary challenge with *Mycobacterim tuberculosis*. *J. Immunol*., 178(11):7222-34. doi:10.4049/jimmunol.178.11.7222
5. Duarte R, Carvalho C, Pereira C, Bettencourt A, Carvalho A, Villar M, Domingos A, Barros H, Marques JA, Pinho Costa P, Mendonça D, Martins B (2011) HLA class II alleles as
6. Etna MP, Giacomini E, Severa M, Coccia EM (2014) Pro- and anti-inflammatory cytokines in tuberculosis: a two-edged sword in TB pathogenesis. *Semin.*

Immunol., 26:543-51. doi:10.1016/j.smim.2014.09.011

7. Peresi E, Oliveira LRC, Silva WL, Nunes da Costa, ÉA P João, PAJ Ayres, JA Fortes, MRP Graviss, EA Pereira, AC Calvi SA (2013) Cytokine Polymorphisms, Their Influence and Levels in Brazilian Patients with Pulmonary Tuberculosis during Antituberculosis Treatment. Tuberculosis Research and Treatment, 13.
8. Hussain S, Afzal N, Javaid K, Ullah MI, Ahmad T, Uz-Zaman S (2010) Level of Interferon Gamma in the Blood of Tuberculosis Patients. Iran. J. Immunol., 7: 4.
9. Shahemabadi AS, Hosseini AZ, Shaghasempour S, Masjedi MR, Rayani M, Shams M, Esphandyari N, Pouramiri M (2010) IL-10 and IL-12 Production in Response to Mycobacterium Tuberculosis Total Lipid Antigens in Multidrug-Resistant Tuberculosis. Iran. J. Immunol., 7:1.
10. Abe M, Akbar F, Matsuura B, Horiike N, Onji M (2003) Defective antigen-presenting capacity of murine dendritic cells during starvation. *Nutrition,* 19:265-9. doi:10.1016/S0899-9007(02)00854-7
11. Wintergerst ES, Maggini S, Hornig DH (2006) Immuneenhancing role of vitamin C and zinc and effect on clinical conditions. Ann Nutr. Met., 50: 85-94.
12. Vilchèze C, Hartman T, Weinrick B, Jacobs WR Jr (2013) *ycobacterium tuberculosis* is extraordinarily sensitive tokilling by a Vitamin C- induced fenton reaction. Nat. Commun., 4:1881.
13. Haertel C, Strunk T, Bucsky P, Schultz C (2004) Effects of vitaminCon intracytoplasmic cytokine production in human whole blood monocytes and lymphocytes. Cytokine 27, 101-106.
14. Boloorsaz MR, Soheila K, Ail RM, Safavi A, Ail AV (2007) Impact of anti-tuberculosis therapy on plasma zinc status in childhood tuberculosis. J. Eastern Med. Health, 13(5): 1078-1084. Iran.
15. Robert K, Murray Daryl, K Granner, Peter A, Maye's Victor, W Rodwell (2003) Acute phase reactants. Harpers Biochemistry Lange Medical book 26th edition 583.
16. Ramesh, RakeshMudaraddi, Ravindra Maradi (2012) Serum Ceruloplasmin Albumin Ratio as a Biochemical Marker to Assist the Diagnosis, Treatment and Prognosis of Pulmonary Tuberculosis Patients, RJPBCS., 3 (2): 494-499.
17. Rafi A, Amir G, John S (2010) Copper and zinc Status serum in childhood pulmonary tuberculosis. Research center for TB and pulmonary disease of Tabriz University, Iran.
18. Ramakrishnan K, Rajaiah S, Karuppusamy K, Uma A, Ramakrishnan B (2008) Serum zinc and albumin levels in pulmonary tuberculosis patients with and without HIV. J. Infect Dis., 61: 202-204.
19. Reza BM, Khalilzadeh S, Milanifar AR, Hakimi SS, Khodayari AA (2007) Evaluation of copper , zinc and copper/zinc ratio in serum of pulmonary tuberculosis children . Pediatric pulmonary ward, national research in statute of tuberculosis and lung disease, Shaheed Beheshti University of Medical Sciences, Iran.
20. Karyadi E, Clive EW, Werner S, Ronald HHN, Rainer G (2002) A double-blind, placebo-controlled study of vitamin A and zinc supplementation in persons with tuberculosis in Indonesia: effects on clinical response and nutritional status. J. Clin. Nutri., 75(4): 720-727.
21. Taneja NK, Dhingra S, Mittal A, Naresh M, Tyagi JS (2010) *ycobacterium tuberculosis* transcriptional adaptation, growth arrest and dormancy phenotype development is triggered by Vitamin C. PLoS One, 5:e10860.
22. Pieters S (2008) Characterization of Human Cellular Immune Responses to Novel *Mycobacterium tuberculosis* Antigens Encoded by Genomic Regions Absent in *Mycobacterium bovis* BCG. Infectious Immunology, 76(9): 4190-4199.
23. Abbas AK, Jens L, Birgit K, Vijaya N (2004) T cell tolerance and auto immunity. Autoimmunity Reviews, **3**: 471-475.
24. Al-Saadi MAK, Muhsin MA, Al-Jubouri AMS (2011) Effect of measles infection on cellular immunity in tuberculosis patients. Journal of Clinical Immunology and Immunopathology Research. 3(2): 22-24.

25. Barry CE, 3rd Boshoff HI, Dartois V, Dick T, Ehrt S, Flynn J, et al (2009) The spectrum of latent tuberculosis: rethinking the biology and intervention strategies. Nat. Rev. Microbiol., 7: 845-855.

26. Schoenborn JR, Wilson CB (2007) Regulation of interferon-gamma during innate and adaptive immune responses. Adv. Immunol., 96: 41-101.

27. Chalifour A, Jeannin P, Gauchat JF, Blaecke A, Malissard M, N' Guyen T, et al (2004) Direct bacterial protein PAMP recognition by human NK cells involves TLRs and triggers alpha-defensin production. Blood 104:1778-1783.

28. Cooper MA, Fehniger TA, Caligiuri MA (2001) The biology of human natural killer-cell subsets. Trends Immunol., 22: 633-640.

29. Lunemann A, Tackenberg B, DeAngelis T, Barreira R, Messmer B, Liliana D, Aaron M, Brian A, Fred D, Jan D, Christian M (2011) Impaired INF-production and proliferation of NK cells in Multiple Sclerosis. International Immunology, 23 (2):139-148.

30. Al-Jubouri AMS (2010) Studying the Effect of Some Factors on Cellular Immunity in Tuberculosis Patients. M.Sc. Thesis. College of Medicine, University of Babylon. Iraq.

31. Martineau AR, Sandra MN, Katalin AW, Beate K, Bridget MH (2007) Neutrophil-mediated innate immune resistance to Mycobacteria. J. Clin. Investigation, 117(7): 1988-1994.

