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Original article

Changes of Zinc Copper and Cu/Zinc ratio and impaired nutritional status in tuberculosis patients of Urmia, Northwest Iran

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Summary. 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 TB compared with that of healthy controls in Urmia, Iran. In a case-control study, 52 patients aged 17–86 y with untreated TB were compared with 58 healthy controls selected from neighbors of the patients. Anthropometric, clinical, serum biochemical and micronutrient status data were collected. Compared to controls, TB patients had significantly lower concentrations of serum albumin, Total iron-binding capacity, ferritin, and calcium ($p<0.05$). Serum zinc concentrations were significantly lower in patients than controls ($p= 0.04$). The average serum levels of copper and zinc in healthy volunteers were 3.90±2.17 and 17.04±2.85 μg/dL, respectively. In tuberculosis patients, serum copper and zinc levels were 5.03±2.93 μg/dL and 16.46±3.17 μg/dL, respectively. Patients showed significantly higher serum copper level than controls ($p= 0.01$). The serum Cu/Zn ratio was significantly higher in the serum of TB patients, (0.30 vs 0.23, $P=0.05$). In conclusion, the nutritional status of patients with TB was poor compared with healthy subjects. Low level of serum Zn in patients with tuberculosis signifies importance of nutritional assessments, in particular micronutrients, for better management of TB.

Key words: malnutrition, micronutrients, tuberculosis

Introduction

Tuberculosis (TB) is a lethal infectious disease caused usually by *Mycobacterium tuberculosis* (1), a small aerobic non-motile bacillus, which usually attacks the lungs but can also affect other parts of the body (2). Despite, TB incidence falling globally for several years and fell at a rate of 2.2% between 2010 and 2011, yet TB remains a major global health problem (3). It causes ill-health among millions of people each year and ranks as the second leading cause of death from an infectious disease worldwide, after the human immunodeficiency virus (HIV) (4). In 2007, there were an estimated 13.7 million chronic active (5), and in 2011, there were an estimated 8.7 million new cases of TB and 1.4 million people died from TB, mostly in developing countries which 7.7% of estimated number of cases in 2011 occurred in the Eastern Mediterranean Region (4).

TB is a contagious disease related to poverty, under-nutrition and poor immune function. People with active tuberculosis are often malnourished and suffer from micronutrient deficiencies as well as weight loss and decreased appetite. Malnutrition increases the risk of progression from TB infection to active TB disease. Food insecurity and poor general nutritional status of the population are important contributors to the global burden of TB disease (6). Malnutrition is an important risk factor for the development of tuberculosis and

may predispose people to the development of clinical disease. Conversely, TB can result in malnutrition and malnutrition weakens immunity, thereby increasing the likelihood that latent TB will develop into active disease. Some micronutrient deficiencies depress cell-mediated immunity, the key host defense against tuberculosis (7).

Yet, little is known about effective nutritional management, nor of the interactions between TB treatment and nutritional status. Considering the lack of information available on dietary intakes of TB patients in Iran, nutritional status assessment of the TB patient is performed to classify nutritional status, identify nutritional risk and to serve as a baseline for monitoring nutrition support adequacy. Identification of nutritional risk indicates the need for nutrition support to maintain body functions and to facilitate recovery. The present study was conducted to find out nutritional factors contributing to the development of TB in Iran.

Subjects and methods

Study setting and subjects

The study was conducted at the Urmia district, prefectural capital of west Azererbayjan Province, north west Iran. The patients (n=52) were all those covered by national tuberculosis management program. Fifty-eight healthy subjects with no history of pulmonary TB, served as the control group, were randomly selected from near-by residents of every individual patient. To elucidate reference levels of micronutrients tested in the community, equal numbers of healthy individuals were recruited from pairs and carefully matched for age, sex, marital status and other relevant variables.

At enrolment, a structured questionnaire was used to collect information on basic demographic data, type of pulmonary TB, length of symptoms before diagnosis of TB was made, belief in avoiding certain food types when coughing, income per month and immediate family size. The height (h) of the patients was measured while standing erect without shoes; weight (w) was measured on a digital standing scale with minimal clothing on.

Biochemical measurements

Ten ml of blood samples were collected from fasting subjects via venipuncture to proceed all analysis. Serum total protein and albumin were analyzed using the biuret and bromocresol green methods, respectively (Randox laboratories, U.K) following manufacturer's instructions. Ferritin was measured using a commercial ELISA kit (IBL-Hamburg, Germany) according to the guidelines of the manufacturer. Total Iron Binding Capacity (TIBC) was measures using a kit from Darman kav company (Tehran, Iran). Iron and calcium was measured using an atuoanalyzer (BT2000, Biotechnica Instruments, Rome, Italy). Copper and zinc were determined by atomic absorption spectrometry, after the digestion of tissue with nitric and perchloric acids, using established procedures (19). Measurements were made at 213.9 and 324.7 nm for zinc and copper, respectively.

Data analysis

A one-sample Kolmogorov-Smirnov test was used to check whether data were normally distributed. Mean and standard deviation are used for reporting normally distributed data. An independent sample t test was used to assess the differences between patients and controls. A P value < 0.05 was considered significant. Analyses were performed using SPSS software, version 11.5 (SPSS, Chicago, Illinois, USA).

Results

Demographic findings

As shown in Table 1, out of 52 patients, 51 (98.08%) were older than 20. Among 52 patients there were 22 (42.31%) males and 30 (57.69%) females. Among 58 healthy subjects there were 30 (51.72%) males and 28 (48.28%) females. Patients and healthy subjects ranged in age from 17 to 86 (mean age, 50.2 ± 20.23 years) and 15 to 90 years (mean age, 41.12 ± 18.11 years), respectively.

Patients were from both rural and urban area. Of the patients, 88.46% were un- or low lettered (under high school level). More than half of the patients (55.77%) were recognized as belonging to families with poor economic status. Significant increased body

Table 1: Demographic characteristics of patients

	Memale	Fale	Total
Number	22	30	52
Age (year):			
<20		1 (3.33%)	1 (1.92%)
20-40	9 (40.91%)	7 (23.33%)	16 (30.77%)
41-60	8 (36.36%)	8 (26.67%)	16 (30.77%)
>60	5 (22.73%)	14 (46.67%)	19 (36.54%)
Resident:			
Rural	10 (45.45%)	17 (56.67%)	27 (51.92%)
City	12 (54.55%)	13 (43.33%)	25 (48.08%)
Literature:			
Unlettered	10 (45.45%)	23 (76.67%)	33 (63.46%)
Elementary	5 (22.73%)	2 (6.67%)	7 (13.46%)
Guidance	5 (22.73%)	1 (3.33%)	6 (11.54%)
High school	1 (4.55%)	4 (13.33%)	5 (9.62%)
College	1 (4.55%)	0	1 (1.92%)
Economic status:			
Desirable			3 (5.77%)
Intermediate			20 (38.46%)
Poor			29 (55.77%)
Housing Status:			
Leased			7 (13.45%)
Personal property			45 (86.54%)
Diseases categories:			
Smear-positive pulmonary	15	18	33 (63.46%)
Smear- negative pulmonary	1		1 (1.92%)
Outside the lung	6	12	18 (34.62%)
Anthropometric status:			
Initial weight (kg)	60 ± 12.6	61.1 ± 13.3	60.6 ± 12.9
Current weight (kg)	63.4 ± 12.6	62.3 ± 13.9	62.8 ± 13.3***
Height (cm)	173 ± 9.8	157 ± 5.8	164 ± 10.9
BMI (kg/m2)	21.3 ± 3.6	25.2 ± 5.6	23.6 ± 5.2

Anthropometric data are expressed as mean ± SD
****P < 0.001 (independent sample t test)*

weight was observed in 59.62% of patients during treatment periods.

Clinical findings

Of the patients, 63.46% were recorded as smear-positive pulmonary, 1.92% was smear-negative pulmonary and 34.62% with tuberculosis outside the lung. Fever, cough for more than two week, phlegm, bloody phlegm, weight loss, appetite loss, lethargy, **night sweats**, and fatigue were recorded for 61.54% (32), 63.46% (33), 55.77% (29), 15.38% (8), 46.15% (24), 42.31% (22), 26.92% (14), 38.46% (20) and 46.15% (24), respectively.

Laboratory findings

As shown in Table 2, patients with tuberculosis had significantly lower serum albumin levels as compared to controls. Serum total protein level did not differ between two groups of patients and controls. On whole, patients had significantly lower serum levels of TIBC compared to controls (p= 0.0005). This reduction was observed for women (p= 0.01) and men (p= 0.007) with tuberculosis, separately, as compared to women and men in control group. Serum Ferritin levels were significantly higher in patients group compared to controls (p= 0.03).

Table 2. Serum levels of selected biological and hematologic indices of TB patients and healthy matched individuals

Parameters	Patients	Controls
Alb (g/dl):		
Males	5.05 ± 0.49	5.32 ± 0.44*
Females	4.86 ± 0.49	5.06 ± 0.48
Total	4.95 ± 0.49	5.20 ± 0.47**
Total protein (g/dl):		
Males	8.53 ± 0.69	8.51 ± 0.72
Females	8.43 ± 0.80	8.52 ± 0.80
Total	8.48 ± 0.75	8.52 ± 0.75
Iron (µg/dl):		
Males	96.67 ± 35.19	110.03 ± 42.12
Females	89.33 ± 39.20	84.18 ± 32.94
Total	92.78 ± 37.18	97.55 ± 39.83
TIBC (µg/dl):		
Males	338.08 ± 64.72	378.87 ± 53.62**
Females	348.44 ± 65.14	384.14 ± 66.42*
Total	343.57 ± 64.50	383.83± 59.83***
Ferritin (ng/ml):		
Males	122.19 ± 106.71	88.04 ± 55.30
Females	99.61 ± 129.94	61.37 ± 77.07
Total	110.24 ± 118.97	74.94 ± 67.63*
Ca (mg/dl):		
Males	9.72 ± 0.51	9.93 ± 0.40*
Females	9.68 ± 0.41	9.80 ± 0.38
Total	9.7 ± 0.45	9.86 ± 0.39*

*Values are expressed as mean ± SD. Asterisks indicate significant difference between patients and controls. * P , 0.05; ** P , 0.01; *** P , 0.001 (independent sample t test)*

Micronutrients status

As shown in the Figure 1 serum iron concentration did not differ significantly between two groups, but serum zinc (p= 0.04) and calcium (p= 0.02) concentrations were significantly lower in patients than controls. The average serum levels of of copper and zinc in healthy volunteers were 3.90±2.17 and 17.04±2.85 µg/dL, respectively. In tuberculosis patients, serum copper and zinc levels were 5.03±2.93 µg/dL and 16.46±3.17 µg/dL, respectively. Patients showed significantly higher serum copper level than controls (p= 0.01). The serum Cu/Zn ratio in patients was significantly higher than healthy subjects, (0.30 vs 0.23, P=0.05).

Discussion

We observed that most of the patients had low schooling and were from poor social stratum. There is substantial evidence, on a national level, that suggests positive association between social and economic indicators and TB (8, 9). Poverty has been documented as a serious determinant of TB, both at the macro-scale

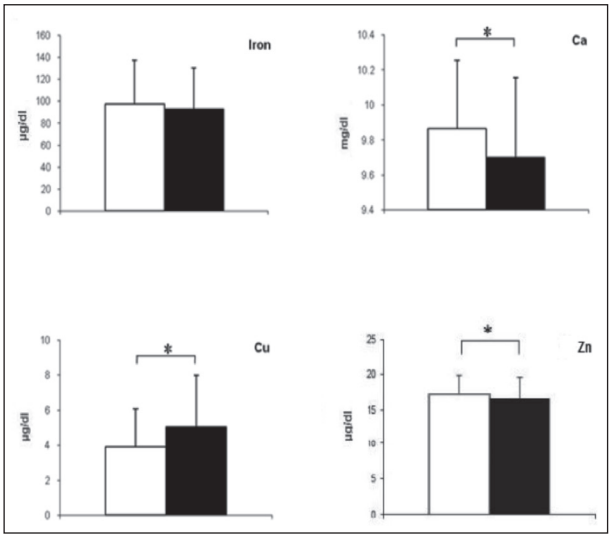

Figure 1. Serum levels of calcium, iron, copper and zinc in TB patients (black bar) and healthy controls (white bar). Data are expressed as mean ± SD. Significance of differences was tested with the independent sample t test. * indicates P< 0.05.

and in individual level. A linear association has been reported between per capita gross domestic product and TB incidence from previous studies (10). Most analyses of data have confirmed the positive association between household and area poverty indicators and TB in such diverse settings as South Africa (11), Brazil (12), Vietnam (13) and Zambia (14). These data imply that the targeting of interventions to the most vulnerable groups may be necessary to speed progress toward elimination of this scourge.

In the present study, patient's current weight was significantly greater than their initial weight. Several studies have shown that anthropometric indicators improve during tuberculosis chemotherapy. A study conducted in Malawi showed that among 1181 adults with tuberculosis, weight significantly increased after 4 weeks of treatment (15). This is most likely for a variety of reasons including improved appetite and food intake, reduced energy/nutrient demands, and improved metabolic efficiency.

The link between tuberculosis and malnutrition consists of two interactions: the effect of tuberculosis upon nutritional state, and the effect of malnutrition on the occurrence and clinical manifestations of tuberculosis. Several studies have examined the effect of tuberculosis on nutritional state and demonstrated extensive nutritional depletion at the time of diagnosis. Nutritional alterations in tuberculosis include increased energy expenditure, nutrient malabsorption, micronutrient malnutrition, and increased production of inflammatory cytokines with lipolytic and proteolytic activity (16).

Serum albumin is an indicator of body protein status. Many studies have reported low concentrations of serum albumin (<35g/L) at the time of active TB diagnosis (17-19). In harmony with the previous reports, we found low albumin level in patients compared to healthy controls. Since, total protein level did not differ between the two groups; therefore, low levels of albumin may reflect the presence of inflammation rather than a protein deficient state (20).

Tuberculosis is one of two common causes of anemia of inflammation. The clinical manifestations of anemia of inflammation include depressed serum iron levels in spite of adequate iron stores, decreased TIBC and increased ferritin. The anemia results from a host-defense mechanism designed to sequester iron from the invading pathogens and making iron less available to microbes. In the current study, serum levels of iron non-significantly and TIBC significantly was low, while ferritin was notably high in TB patients compared to normal controls. The findings indicated the presence of the anemia and were consistent with previous reports (21).

Throughout the world, poor nutritional status is more common in people with active tuberculosis than in people without tuberculosis (22). Tuberculosis may lead to micronutrient deficiencies by increasing energy requirements, changing metabolic processes, and by decreasing appetite, causing a reduction in food intake (23). The results of present study revealed that TB patients had decreased serum levels of zinc and calcium, but enhanced copper as compared to healthy controls. The findings are in accordance to previous reported findings (24-30). Presence of nutritional and absorptional problems in the patients may lead to the nutrient deficiencies. The decline in serum zinc was probably due to redistribution of zinc from serum to other tissues (31) or reduction of zinc-carrier proteins and or a rise in the production of metallothionein, a protein that transports zinc to the liver (32). Elevated copper may due to zinc deficiency, whereas zinc and copper have an intimate relationship; each one balancing the other one out. It has long been known that zinc is needed to form ceruloplasmin and metallothionein (26), which are needed to bind to copper to carry it into the mitochondria.

According to table 3, serum Zn and Cu levels in patients with tuberculosis in current study were lower than other studies. This may lead to low Cu/Zn ratio in comparison to other studies. The serum Cu/Zn ratio was also studied for several diseases (29). In this study, it was found that the serum Cu/Zn ratio in patients with tuberculosis was significantly higher when compared with healthy subjects, (0.30 vs 0.23, P=0.05). Overall, Elevated Cu levels and Cu/Zn ratio and decreased Zn levels were found in all studies.

Hypercalcaemia was detected in 25% Greek (33) and Swedish (34), 16% to 28% United States (35), 27.5% Malaysian (36), 6% Hong Kongs (37) patients with pulmonary tuberculosis. Hypocalcaemia has also been reported in 38% Japanese (38) and Pakistani (39) patients. Similar results were also found in Egyptian (40), Nigerian (41) and Indian (42) patients. Abnormalities in calcium metabolism have not been studied

Table 3. Comparison of means concentrations of serum Zinc, Copper , Cu/zinc ratio in study subjects with other Studies

Zinc (μg/dl)	Copper (μg/dl)	Cu/zinc	References
16.68±2.85	5.03±2.93	0.30±0.19	This study
87.27±26.88	187.95±50.48	2.38±0.98	-24
64.14±3.97	123.65±9.98	-	-25
118.48±12.83	107.79±21.25	0.92±0.21	-28
54.09±14.16	139.36±48.32	4.36±1.12	-29
59.94±10.96	173.35±36.50	-	-30

in our population of Pulm TB. Presence of hypocalcaemia was observed in studied patients. The discrepancy in our findings and those from US and Europe could be explained by many factors e.g. ethnic differences, malnutrition and malabsorption associated with our patients of Pulm TB. Presence of nutritional and absorptional problems as evident form concomitant finding of hypophophataemia could be a part of the same disease process or could be due to coexisting gastrointestinal disease.

Conclusion

The nutritional status of patients with active TB is poor when compared with healthy controls. A remarkably lower serum Zn levels in patients with tuberculosis than healthy subjects signifies importance of nutritional assessments, in particular micronutrients, for better management of TB. Thus, it is concluded that dietary interventions to improve nutritional status of under treatment patients should be considered as necessary component of any TB control program within the society.

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