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THE DIFFERENCE OF SERUM ZINC LEVELS ON THE INTENSIVE AND CONTINUATION PHASE OF CHILDHOOD TUBERCULOSIS TREATMENT

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ABSTRACT

BACKGROUND: Zinc deficiency (serum zinc levels of ≤65 µg/dl) leads to increase susceptibility to infection and known to impair cellular mediated immunity which plays an important role in tuberculosis (TB).

OBJECTIVE: To evaluate serum zinc levels and nutritional status of the tuberculous children on the intensive and continuation phase of TB treatment.

METHODS: This was a cohort-prospective study whereas serum zinc levels and nutritional status of 29 children with various form of TB were measured on the intensive and continuation phase of TB treatment.

RESULTS: Mean serum zinc levels in children with pulmonary TB (n=21) was 59.2 µg/dl (15.02), lymphadenitis TB (n=3) was 59.0 µg/dl (10.44), and meningitis TB (n=5) was 53.2 µg/dl (18.36) on the intensive phase of TB treatment. Serum zinc levels measured on the intensive and continuation phase were 58.1 µg/dl (14.93) and 68.9 µg/dl (16.40), respectively, and significant rise in serum zinc levels was noted (mean increment of serum zinc levels=10.8 µg/dl; P<0.001). Despite of significant rise in serum zinc levels, the proportion of tuberculous children with zinc deficiency state remained high (15/29). The proportion of tuberculous children with malnutrition was decreased from 24/29 to 16/29. There was no association between serum zinc levels and nutritional status in the sample population.

CONCLUSION: Increase of serum zinc levels is demonstrated along the phase of TB treatment, nevertheless the proportion of tuberculous children with zinc deficiency state remains high. Further studies regarding zinc supplementation in childhood TB are warranted.

KEYWORDS : childhood tuberculosis; intensive and continuation phase; nutritional status; serum zinc levels

INTRODUCTION

The United Nations (UN) delivers particular attention to eradicate tuberculosis (TB) disease through The Sustainable Development Goals (SDGs) with goal 3: good health and well-being, in which one of its target is by 2030, end the epidemics of TB.[1] In 2015, there were 710.000 world population died of TB and there were 10.4 million of newly-diagnosed cases worldwide, whereas 10% of cases were childhood tuberculosis.[2]

Majority of childhood tuberculosis contracting the disease from TB adult cases. After inhaling *Mycobacterium tuberculosis*, a portion of children may develop latent tuberculosis infection. The subsequent development of clinical disease is determined by the interaction of the host and the organism, and is highly age dependent, whereas children <5 years old pose higher risk to develop TB disease.[3]

Tuberculosis drug regimens consist of two phases – the intensive (two-months duration) and continuation (four to ten-months duration) phase. The duration and the TB drug regimens depend on the TB diagnostic category.[4]

Zinc deficiency (serum zinc levels ≤ 65µg/dl) has been commonly observed in patients with TB. Zinc is known to be essential for highly proliferating cells in the human body, especially the immune system. Various kinds of immune cells show decreased function after zinc depletion.[5] Zinc deficiency impairs the immune system, especially cellular immune response which plays an important role in TB disease.[6]

The causes of low serum zinc levels in childhood tuberculosis are multifactorial. In TB infection, zinc redistribution to the liver for the synthesis of acute phase reactant occurs, hence serum zinc levels will decrease. Zinc as a trace element also being utilize for the growth and multiplication of the *Mycobacterium*.[7] Malnutrition is closely related to childhood TB and the low micronutrient levels may affect the host immune response.[8]

Several studies showed that serum zinc levels were significantly lower in TB patients as compared to healthy controls. Subsequently, serum zinc levels will increase along the period of TB treatment.[9-11] The objective of this study was to evaluate the serum zinc levels and nutritional status of the tuberculous children on the intensive and continuation phase of TB treatment.

METHODS

This study was approved by the Health Research Ethical Committee, Medical Faculty of University of Sumatera Utara/Haji Adam Malik General Hospital, Medan, North Sumatera. An analytic observational study with a cohort prospective design was performed at Haji Adam Malik General Hospital and University of Sumatera Utara Hospital from Mei to October 2018. The inclusion criteria was newly-diagnosed tuberculous children aged 6 months to 18 years old on the intensive phase of TB treatment. The exclusion criteria were immunocompromised children (severe malnutrition, HIV infection and malignancy), previous TB treatment, poor compliance to the regimen, intake of zinc supplementation within the last one month, compromised liver and kidney function. Informed consent was obtained from all parents of the subjects prior to subject enrollment.

Characteristics of the subjects including sex, age, nutritional status, history contact with adult TB patient, clinical symptoms, radiological findings, rapid test molecular MTB/RIF analysis and form of TB were documented. The nutritional status of the subjects were plotted according to weight for length chart from WHO Child Growth Standard 2006 for subjects under 5 years old and CDC 2000 growth chart for subjects 5-18 years old. Initial serum zinc levels were measured on the intensive phase of TB treatment and subsequently after minimum duration of two months when patient already on the continuation phase. Measurement of serum zinc levels were performed with inductively coupled plasma mass spectrometry (ICP-MS). Classification of serum zinc levels was deficiency (≤65 µg/dl) and normal (66 – 150 µg/dl) state.

Bivariate analysis was used to determine the association between serum zinc levels with phase of TB treatment and the association

between serum zinc levels with nutritional status of tuberculous children during phase of TB treatment. Bivariate analysis was performed with Wilcoxon signed-rank test and independent t-test by SPSS Statistics ver. 20.0. Statistical significance was considered at P value <0.005.

RESULTS

There were 31 tuberculous children who met the inclusion criteria, with 2 children drop-out during study period due to refusal to undergo measurement on the continuation phase and received zinc supplementation. Therefore, 29 children accomplished the study. Patient characteristics are summarized in Table 1. The mean age of the patient was 112.2 months (SD53.30) with predominance age group of >10 years old. The nutritional status of 24/29 patients were moderate malnutrition. Most of the patient had contact with adult TB patient. The common clinical symptom(s) include weight loss (27/29), fever > 2 weeks (25/29), malaise (23/29), and cough (21/29). The most prominent chest radiological finding was infiltrates with hilar lymphadenopathies (16/29). Rapid test molecular MTB/RIF was performed on 8 patients, which revealed MTB positive RIF sensitive. Regarding the form of TB, pulmonary TB, meningitis TB and lymphadenitis TB were composed of 21, 5 and 3 patients, respectively.

Mean serum zinc levels associated with form of TB and duration of intensive phase TB treatment was shown on Table 2. The lowest mean serum zinc levels on the intensive and continuation phase TB treatment were on meningitis TB (53.2 µg/dl (SD 18.36) and 65.0 µg/dl (SD 14.91), respectively.

Initial mean serum zinc levels measurement on the intensive phase was 58.1 µg/dl (SD 14.93), with minimum and maximum values were 21 and 92 µg/dl, respectively. After minimum duration of two months, the second measurement of mean serum zinc levels on the continuation phase was 68.9 µg/dl (SD 16.40), with minimum and maximum values were 42 and 120 µg/dl, respectively. The mean increment of serum zinc levels on the intensive and continuation phase was 10.8 µg/dl with *P*<0.001 (Table 3). All of the patients had increment of serum zinc levels on the period of TB treatment (Figure 1). The minimum and maximum increment of serum zinc levels were 2 and 33 µg/dl, respectively.

Table 1. Characteristics of the patients

Characteristics	
Sex (n)	
Male	12
Female	17
Age (year) (n)	
1-5	7
>5-10	10
>10	12
Nutritional status (n)	
Well nourished	5
Moderate malnutrition	24
Contact with adult TB patient (n)	
Yes	24
No	5
Clinical symptom(s)* (n)	
Fever >2 weeks	25
Cough >2 weeks	21
Malaise	23
Weight loss	27
Loss of consciousness	5
Seizure	5
Enlargement of lymphnode(s)	3
Chest radiological findings (n)	
Infiltrates	4
Hilar lymphadenopathies	7
Infiltrates with hilar lymphadenopathies	16
Pleural effusion	1
Normal	1
Results of rapid test molecular MTB/RIF	
MTB negative	0
MTB positive RIF sensitive	8
MTB positive RIF resistant	0
Not available	21
Form of TB (n)	
Pulmonary TB	21
Meningitis TB	5
Lymphadenitis TB	3

***) One patient may develop more than one clinical symptom(s)**

Table 2. Mean serum zinc levels according to form of TB and duration of intensive phase TB treatment

Parameter(s)	Mean serum zinc levels on intensive phase (µg/dl) (SD)	Mean serum zinc levels on continuation phase (µg/dl) (SD)
Form of TB		
Pulmonary TB	59.2 (15.02)	69.4 (18.04)
Lymphadenitis TB	59.0 (10.44)	71.6 (6.54)
Meningitis TB	53.2 (18.36)	65.0 (14.91)

Table 3. Mean increment of serum zinc levels along intensive and continuation phase of TB treatment

Parameter(s)	Mean serum zinc levels (µg/dl) (SD)	Mean increment of serum zinc levels (µg/dl)	*P*
Intensive phase	58.1 (14.93)	10.8	< 0.001
Continuation phase	68.9 (16.40)		

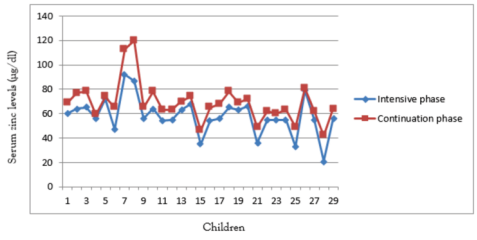

Figure 1. Serum zinc levels on the intensive and continuation phase of TB treatment

There were 23 patients and 15 patients with zinc deficiency state (serum zinc levels ≤65µg/dl) on the intensive (Figure 2A) and continuation (Figure 2B) phase, respectively. Based on anthropometric measurements on the intensive and continuation phase TB treatment, there were 24 and 16 patients with moderate malnutrition, respectively (Figure 3). All of the patients had gained body weight and height.

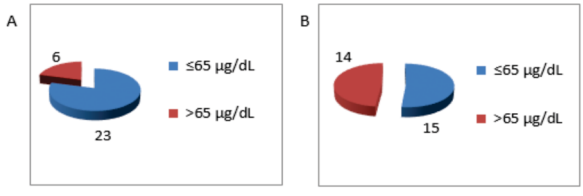

Figure 2. Proportion of zinc deficiency state on the intensive (A) and continuation (B) phase of TB treatment

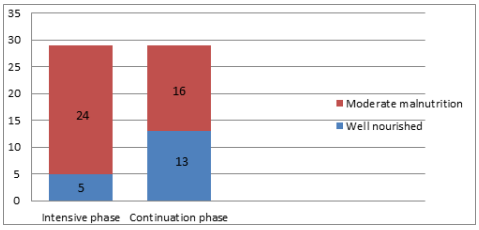

Figure 3. Proportion of nutritional status of the patients during intensive and continuation phase of TB treatment

Mean serum zinc levels of well-nourished and moderate malnutrition patients on the intensive phase were 55.2 µg/dl (SD12.20; 95%CI=39.9-70.4) and 58.7 µg/dl (SD15.54; 95%CI=52.2-65.3), P=0.633. While on the continuation phase, mean serum zinc levels of well-nourished and moderate malnutrition patients were 70.8 µg/dl (SD23.39; 95%CI=56.7-84.9) and 67.3 µg/dl (SD7.84; 95%CI=63.1-71.4), P=0.610. Based on the statistical analysis, there was no association between serum zinc levels and nutritional status during intensive and continuation phase of TB treatment (Table 4).

Table 4. Association of serum zinc levels with nutritional status during intensive and continuation phase of TB treatment

Parameter(s)		Mean serum zinc levels (µg/dl) (SD)	95%CI	P
Nutritional status on the intensive phase	Well-nourished	55.2 (12.20)	39.9 – 70.4	0.633
	Moderate malnutrition	58.7 (15.54)	52.2 – 65.3	
Nutritional status on the continuation phase	Well-nourished	70.8 (23.39)	56.7 – 84.9	0.610
	Moderate malnutrition	67.3 (7.84)	63.1 – 71.4	

DISCUSSION

Zinc plays an important role in innate and adaptive immunity systems. Normal serum zinc levels in pediatric population is 70-150 µg/dl, with cut-off value for zinc deficiency state is ≤65 µg/dl.[12] The causes for zinc deficiency state in tuberculous children are multifactorial. In TB infection, there is zinc redistribution into the liver in order to synthesize acute phase reactants, therefore the serum zinc levels may decrease. *Mycobacterium tuberculosis* also utilizes zinc for growth and multiplication.[7] Moreover, malnutrition is closely related to TB disease, hence status of micronutrient (zinc) of tuberculous children may be compromised.[8] Recently, zinc deficiency state in tuberculous children was found in several studies.[9-11]

The predominance age group of tuberculous children in our study was >10 years old. One of the risk factor for TB disease is age dependent (below 5 years old).[3] This is possible as not all of the tuberculous children population included in this study, therefore the age group of the sample population is not completely representative.

Along the TB treatment period, there was decrement of moderate malnutrition proportion from 29 to 16 patients. All of the patients had gained weight. Weight gain is one of the indicators of good response to TB treatment, along with other clinical symptoms improvement.[3] History of contact with adult TB patients declared from most of the patient. The most common transmission of TB arises from household contact.[3]

Clinical manifestation in childhood TB is often not specific. Chronic cough is the most common symptom in adult TB, but in childhood TB, cough may not be the typical symptom as the location of primary infection in childhood TB may be on the lung parenchyma where the cough receptor is not located.[13] Our study showed that the most common clinical symptoms were weight loss, followed by fever >2 weeks, malaise and cough. Rapid test molecular MTB/RIF was performed to some of the patients which all revealed MTB positive RIF sensitive. Further investigation on serum zinc levels in multidrug resistant (MDR) TB population is important. Bahi et al concluded that on adult MDR TB population, significant decrease of serum zinc levels also noted. Along the second line TB treatment, the serum zinc levels on the third and sixth month of the treatment were increased.[14]

Pulmonary TB was the most common form of TB noted on our study, followed by meningitis TB and lymphadenitis TB. The common form of extra pulmonary childhood TB are superficial lymph nodes TB and central nervous system TB.[3] Patient with severe form of TB (meningitis TB) had the lowest serum zinc levels. Ray et al found that disseminated TB and meningitis TB had the lowest serum zinc levels compared to other form of TB. The decrease of serum zinc levels is proportional with the severity of TB disease.[9]

Our study revealed the significant increase of serum zinc levels in tuberculous children on the continuation phase. Previous studies also revealed the increase of serum zinc levels during TB treatment. Serum zinc levels may serves as indicator to evaluate the therapeutic response of the treatment.[9,10] The increment of serum zinc levels along the TB treatment suggestive of responsiveness to TB treatment during intensive phase, which is aimed to eradicate the active replicating bacilli.[15] If significant amount of active bacilli is eradicated, the utilization of zinc by the bacilli is decrease, hence the serum zinc level will increase.

Despite of the significant increase of serum zinc levels, most of the patient remained on the zinc deficiency state. This finding is considered due to the extremely low values of initial serum zinc levels in some of the patients, hence despite of the increment, the subsequent measurements of serum zinc levels were still in deficiency state. Therefore, zinc supplementation in childhood TB population could be considered. Zinc supplementation on adult TB population revealed early sputum conversion and early resolution of radiological lesion,[15] enhanced TCD4+ and IFN-γ levels.[6] In childhood TB, Nenni et al found that zinc together with Ω-3 and vitamin A supplementation for one month during the TB treatment significantly increase leptin levels and decrease TNF-α levels.[16]

Javed et al and Asma'u et al found that serum zinc levels in healthy children was higher than the malnutrition children. More severe form of malnutrition associates with lower serum zinc levels.[17,18] Contrary, our study showed that there was no association between serum zinc levels and nutritional status of the children. This finding needs to be confirmed as the tuberculous children with severe malnutrition were excluded and study with larger sample size is needed.

Limitations of this study are no food analysis/food recall performed thus we cannot evaluate the kinds of food and caloric intake. Unfortunately, during our study period, the tuberculin test was not available nationwide, hence we cannot evaluate its association with serum zinc levels. Bertha et al found that tuberculous children with negative tuberculin test showed lower serum zinc levels compared to those with positive results. This warrants the role of zinc in cellular immunity response to the tuberculin test whereas zinc deficiency state may affect the proliferation and activity of T lymphocyte. Our study also did not evaluate completely serum zinc levels from the initial time of diagnosis, transitional point of time from intensive to continuation phase and the end of TB treatment phase.

To conclude, increase of serum zinc levels is demonstrated along the phase of TB treatment, nevertheless the proportion of tuberculous children with zinc deficiency state remains high. Further studies regarding zinc supplementation in childhood TB are warranted.

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