Lower Plasma Selenium Level in Primary Malignant Bone Tumors: A Survey Research

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ABSTRACT

Objective: To compare plasma selenium levels in primary bone tumor patients with clinically healthy Thai subjects.

Materials and Methods: A cross-sectional study on plasma selenium of primary bone tumor patients aged above 12 years old was obtained at Siriraj Hospital. The plasma samples were used for selenium assay by Electrothermal Atomic Absorption spectrometry method. The plasma selenium levels were compared with the clinically healthy Thai subjects or within primary bone tumor groups (age: below or above 30 years, gender: male or female, benign or malignant tumor, metastasis or non-metastasis).

Results: One hundred and nine primary bone tumor patients were included in this study. Plasma selenium level in clinically healthy Thai subjects aged more than 30 years old was significantly higher than a primary bone tumor group (121.71 ± 19.96 µg/L vs 111.88 ± 23.62 µg/L, mean difference -9.83, p-value = 0.017). The plasma selenium levels within the primary bone tumor patients did not exhibit significant differences when compared across genders, age groups below and above 30 years old, benign and malignant tumors, or between metastatic and non-metastatic tumor cases.

Conclusion: A patient with a history of malignant bone tumors tends to have a lower level of plasma selenium than normal people. However, the study of selenium supplementation for those who have a higher risk of developing malignant bone tumors is needed in the future.

Keywords: Selenium; Primary bone tumors; malignancy; metastasis; malignant bone tumor (Siriraj Med J 2024; 76: 333-338)

INTRODUCTION

Selenium (Se) is a nonmetallic element that has chemical and physical activities like Sulfur and Tellurium. Selenium is distributed in several human tissues; approximately 27.5% is localized in skeletal muscle, 16% in the bone, and 10% in blood.[1] Since selenium is an element, it cannot be synthesized in the human body. Therefore, plasma selenium level is dependent on dietary intake. Selenium is found predominantly as selenomethionine and selenocysteine in foods such as bread, cereals, nuts, meat, fish, and other seafood, but the amount and the type of selenium in foods varies greatly and depends on the soil selenium content and composition.[2,3]

Selenium is an integral component of several selenoproteins. The first true selenoprotein identified was glutathione peroxidases (GPXs) which is one of the most important antioxidant enzymes.[4,5] GPXs protect cells against oxidative damage by reducing hydrogen

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peroxide to water and a wide range of organic peroxides with reduced glutathione, preventing lipid peroxidation and cellular damage from reactive oxygen species (ROS), reactive nitrogen species (RNS) and protecting immune cells from oxidative stress.[4-8]

For the time being, the morbidity and mortality rates of primary bone tumors in Thailand are still high due to late detection, delayed referral, and no tumor marker for the screening of bone tumors. Previous studies demonstrate the differences between plasma selenium and several types of cancer such as prostate cancer, bladder cancer[9], and lung cancer.[10] Also, a higher serum selenium level has been shown potential for cancer risk reduction. Therefore, the primary objective of this study is to compare the plasma Selenium level of the patient who was diagnosed with a primary bone tumor with clinically healthy Thai subjects. The secondary objective is to compare the plasma selenium level of patients with younger age (<30 years) and older age (>30 years) groups, type of tumor (benign or malignant) and with and without a history of tumor metastasis.

MATERIALS AND METHODS

Study population

After the ethical committee of Siriraj Hospital approved (COA no. Si 560/2016) the research protocol for this study, primary bone tumor patients aged more than 12 years who had a visit at bone and soft tissue tumor clinic, Siriraj Hospital (as their regular follow-up visit) between September 2016 and August 2017 were informed and consent for this cross-sectional study (the inform and consent were made for with both subjects and at least one of their parent if the subject age lower than 18 years old). The clinically healthy Thai subjects were defined as such based on physical examinations, laboratory tests, and responses to historical questionnaires. Their blood specimens were obtained during a routine check-up program at the National Cancer Institute in Bangkok, Thailand, as previously described.[11] For the primary bone tumor patients, blood samples were collected during their regular follow-up visits after surgical treatment. The diagnosis of a primary bone tumor was confirmed by a histopathological report. We include osteoma, osteoid osteoma, osteochondroma, chondroma, chondroblastoma, chondromyxoid fibroma, synovial chondromatosis, giant cell tumor, fibrous dysplasia, osteofibrous dysplasia, osteosarcoma, chondrosarcoma, fibrosarcoma, and chordoma in this study. The exclusion criterion was a subject with a history of selenium supplementation within 1 year before blood samples were taken.

Sample size calculation

Using the average selenium level from our pilot study and the value for clinically healthy Thai subjects from Attatippaholkun W, et al.[11] alpha = 0.05, and beta = 0.2, 76 patients was calculated to be the minimum number of primary bone tumor patients needed for this study.

Plasma selenium assessment

Plasma selenium assay has been reported elsewhere,[12] briefly, blood samples were collected after a 12-hour-fasting period. Heparinized plasma samples were used for selenium assay by the method of Electrothermal Atomic Absorption spectrometry (ETAAS) with Zeeman background correction with a GTA 110 graphite furnace and PSD-100 autosampler (Varian Australia Pty Ltd., Australia). The instrument parameters were 196.0 nm wavelength, 1.0 nm slit width, co-injection mode, and peak height in measurement mode. All the glassware and plasticware were washed with 5% (V/V) nitric acid, rinsed with ultrapure water, and finally dried at 60°C in a hot air oven. High-quality water, obtained using a Mill-Q system (Millipore), was used exclusively. All the chemicals used were of the highest purity available. All the plasma samples were stored in selenium-free plastic tubes and kept at -20°C until analyzed. Each plasma sample (5ml) was added with a matrix modifier containing 1% (v/v) $NiNO_3$ and 2% (v/v) Triton-X-100, to reach the final concentration of 1,000 mg Ni/ml and 0.1% (v/v) Triton-X-100. Samples were measured in triplicate. Appropriate blank measurements were obtained by repeating the procedure in the absence of the selenium standard solution.

Statistical analysis

Plasma selenium level and demographic data were analyzed by Descriptive statistics in means, standard deviation, 95% CI for mean, number, and percent. Comparison of plasma selenium between primary bone tumor patients and healthy Thai subjects from the previous study.[11] The Shapiro-Wilk test was used for the normality test. For the comparison of the mean, the Student's t-test was used in normally distributed data and the Mann-Whitney U test in non-normally distributed data. All statistical analysis was performed using SPSS version 18 (Chicago: SPSS Inc).

RESULTS

The average plasma selenium level of 109 primary bone tumor patients was 111.59 ± 22.57 µg/L while the

clinically healthy people were 116.94 ± 30.51 µg/L. There was no significant difference in the plasma selenium level between these 2 groups (mean difference = -5.35, p-value = 0.105). when stratified into younger (< 30 years old) and older (≥ 30 years old) age groups, no statistical difference was observed in the younger age group while in the older age group, a significantly lower plasma selenium was observed (121.71 ± 19.96 µg/L vs 111.88 ± 23.62 µg/L, mean difference = -9.83, p-value = 0.017) (Table 1). Regrettably, with the exception of age and gender, no additional demographic data was collected from the subjects. Consequently, this study was unable to compare and present the baseline characteristics of the clinically healthy individuals and the primary bone tumor patients. Among the primary bone tumor patients, no statistically significant differences in plasma selenium levels were observed when comparing between genders (male 115.32 ± 23.33 µg/L, and female 108.76 ± 21.73 µg/L, mean difference = -6.56, p-value = 0.134) (Table 1), age groups (< 30 years 111.08 ± 20.89 µg/L and ≥ 30 years 111.88 ± 23.62 µg/L mean difference = 0.80, p-value = 0.859), benign versus malignant bone tumors (112.35 ± 22.87 µg/L and 110.28 ± 22.26 µg/L, mean difference = -2.07, p-value = 0.647) or the presence versus absence of metastasis (101.92 ± 14.47 µg/L and 112.90 ± 23.19 µg/L mean difference = 10.98, p-value = 0.100) (Table 2).

There was also no statistically significant difference in plasma selenium levels among clinically healthy Thai subjects (116.94 ± 30.51 µg/L)[11] compared to either the benign primary bone tumor group (112.35 ± 22.87 µg/L, mean difference = -4.59, p-value = 0.250) or the malignant primary bone tumor group (110.28 22.26 µg/L, mean difference = -6.66, p-value = 0.189). However, within the primary bone tumor group, the plasma selenium level

TABLE 1. Plasma selenium level of clinically healthy subjects compared to primary bone tumor patients among ages and genders.

Age	Gender	Plasma selenium level (µg/L)[a]		p-value[c]
		Clinically healthy subjects[b]	Primary bone tumor patients	
< 30 years	Male	110.20±22.60 (n = 82)	113.88±22.31 (n = 17)	0.542
	Female	105.14±18.03 (n = 90)	109.00±20.04 (n = 23)	0.372
	p-value[d]	0.105	0.473	
	Total	106.95±19.84 (n = 172)	111.08±24.22 (n = 40)	0.242
≥ 30 years	Male	168.52±46.60 (n = 15)	116.13±24.22 (n = 30)	<0.001
	Female	118.52±17.47 (n = 37)	108.62±22.03 (n = 39)	0.539
	p-value[d]	<0.001	0.193	
	Total	121.71±19.96 (n = 52)	111.88±23.62 (n = 69)	0.017
All	Male	125.22±39.60 (n = 97)	115.32±23.33 (n = 47)	0.115
	Female	112.74±23.76 (n = 127)	108.76±21.73 (n = 62)	0.268
	p-value[d]	0.004	0.134	
	Total	116.94±30.51 (N = 224)	111.59±22.57 (N = 109)	0.105

[a] Mean ± Standard Deviation
[b] Data from Attatippaholkun W, et al.[11]
[c] Comparison between clinically healthy subjects and primary bone tumor patients
[d] Comparison between male and female

TABLE 2. Demographic data of primary bone tumor patients and their plasma selenium level.

	n (%)	Plasma selenium level (µg/L)[a]	p-value
Age group			
< 30 years	40 (36.7)	111.08 ± 20.89	0.859
≥ 30 years	69 (63.3)	111.88 ± 23.62	
Benign/Malignant			
Benign	69 (63.3)	112.35 ± 22.87	0.647
Malignant	40 (36.7)	110.28 ± 22.26	
Metastasis			
Metastasis	13 (11.9)	101.92 ± 14.47	0.100
Non-metastasis	96 (88.1)	112.90 ± 23.19	

[a] Mean ± Standard Deviation

of the malignant bone tumor was significantly lower than clinically healthy subjects (121.71 ± 19.96 µg/L)[11] in the older age group (>30 years) (109.88 ± 22.41 µg/L, mean difference = -11.83, p-value 0.020), especially chondrosarcoma (107.75 ± 22.24 µg/L, mean difference = -13.96, p-value 0.020). There is also a trend to lower plasma selenium levels in osteosarcoma in the advanced age group (102.25 ± 14.43 µg/L, mean difference = -19.46, p-value 0.06) as shown in Table 3.

DISCUSSION

According to the study result, plasma selenium in primary bone tumor patients was not different from the normal average of plasma selenium in the normal Thai population. At the patient age under 30 years old, plasma selenium may not relate to the occurrence of primary bone tumor. However, a patient above 30 years old who was diagnosed with chondrosarcoma, shows lower plasma selenium levels than in the clinically healthy

TABLE 3. Comparison of plasma selenium level between the type of primary bone tumor and clinically healthy Thai subjects in the lower and older age group

	Age < 30 years			Age ≥ 30 years		
	n	Plasma selenium level (µg/L)	p-value[a]	n	Plasma selenium level (µg/L)	p-value[a]
Healthy Thai subject[c]	172	106.95 ± 19.84		52	121.71 ± 19.96	
Benign tumor						
Giant cell tumor	11	111.09 ± 21.79	0.510	28	113.75 ± 25.95	0.130
Fibrous dysplasia	3	106.67 ± 16.62	0.981	9	113.78 ± 26.55	0.299
All benign tumor	26	111.12 ± 20.27	0.320	43	113.09 ± 24.51	0.062
Malignant						
Osteosarcoma	13	109.46 ± 22.96	0.664	4	102.25 ± 14.43	0.062
Chondrosarcoma	1	131.00	N/A	16	107.75 ± 22.24	0.020
All malignant tumor	14	111.00 ± 22.80	0.469	26	109.88 ± 22.41	0.020
All primary bone tumor	40	111.08 ± 20.89	0.242	69	111.88 ± 23.62	0.017

[a] Comparison between clinically healthy subjects and primary bone tumor patients
[b] A value of clinically healthy Thai subject from Attatippaholkun W, et.al.[11]

Thai subjects (p-value < 0.05). This finding aligns with an earlier study[11] that in osteosarcoma plasma selenium level is lower than in the normal population.

Although many pieces of research showed lower levels of plasma selenium in relation to the occurrence of many types of cancer[9,10] and increased risk of cancer mortality.[13] Our cross-sectional study shows that only chondrosarcoma in a patient aged more than 30 years old shows a significantly lower level of selenium compared with the normal population. For the osteosarcoma patient aged more than 30 years, the average selenium level was 102.25 ± 14.43 µg/L seems to differ from clinically healthy Thai subjects in the same age group (121.71 ± 19.96 µg/L). However, we cannot demonstrate a statistically significant difference (p=0.06), which is probably because of our limited subject number in this study.

Several theories demonstrate the mechanism of selenium for cancer prevention. Selenium shows its antioxidant effects through selenoprotein (as selenocysteine[14] helping cell growth and survival. Also, selenium promotes anti-tumor immunity by modulating the immune system such as activating immune cells (e.g. macrophage, T-cells, neutrophil, and NK cells) to reverse the immunosuppressive environment in the tumor headed for anti-tumor immunity, and stimulating of pro-inflammatory cytokines such as IFNγ and TNFα release.[8]

Supplementation of selenium in patients with high risk for several kinds of cancer may have some benefits but there is still no recommendation to give individual high-dose selenium supplements for cancer prevention.[15] Also, no evidence demonstrates that selenium supplementation results in cancer prevention in the human.[16] Too high level of daily intake of selenium may lead to selenosis especially when selenium intake exceeds the Tolerable Upper Intake Level of 400 micrograms per day.[17] Also, there was a study that demonstrated that appropriate selenium levels of less than 130 µg/L were associated with decreased mortality.[18]

There are some limitations of our study. First, a selenium level of clinically healthy Thai subjects was collected at a different time point compared with the primary bone tumor patient. The average selenium level in clinically healthy Thai subjects probably differed since the development of food logistics and food science and technology. However, the mean selenium level of our population is not that much different from the earlier reported mean serum selenium level from the US population (125.6 µg/L).[18] Second, the information about the dietary intake of all patients was not collected and analyzed. Therefore, selenium levels in malignant bone tumor patients probably differed from the clinically healthy group due to poorer oral intake results from the tumor itself or cancer treatment. Third, additional factors that could influence the varying plasma selenium levels of our subjects, such as socioeconomic status (reflecting the ability to purchase selenium-rich foods), educational level (indicating knowledge regarding dietary choices), and geographic location (impacting soil selenium content), were not captured in our data collection. The plasma selenium levels observed in our study may have differed if these parameters were taken into account for correction.

CONCLUSION

A group of patients with a history of malignant bone tumors tend to have a lower level of plasma selenium compared with the general Thai population. These could imply that selenium may be needed for the prevention of malignant bone tumors. The study of selenium supplementation for people who have a high risk for malignant bone tumors should be performed. In order to demonstrate the efficacy and the pathophysiology of selenium in malignant bone tumors.

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Conflict of interest statement

The authors declare that they have no competing interests.

Author contributions

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