Jacobs Journal of Cancer Science and Research

OPEN ACCESS

Original Article

Level of Selenium of Children with Acute Lymphoblastic Leukemia (ALL)

M.H. Mousazadeh[1*], S. Goharkhani[1], F. Ghazizadeh[2]

[1]Department of Chemistry, Amirkabir University of Technology, Tehran, Iran

[2]Department of Urmia University of Medical Sciences, Urmia, Iran

*Corresponding author: MH Mousazadeh, Department of Chemistry, Amirkabir University of Technology, Tehran, Iran; E-mail: mousazadeh@aut.ac.ir

Received Date: 03-08-2019

Accepted Date: 03-27-2019

Published Date: 04-02-2019

Abstract

Essential elements, mainly selenium were involved in protection against oxidative stress in cells. Oxidation could lead to the formation of free radicals that have been implicated in the pathogenesis of many diseases, including leukemia. Leukemia is a neoplastic disease that is susceptible to antioxidant enzyme and essential elements alterations. In this study, serum selenium, was measured by atomic absorption spectrometry in the children with ALL, without any prior treatment (new case, n=30), patients receiving treatment (n=30), and patients completely cured after chemotherapy (as the control group) (n=30). Selenium was found to be significantly lower in leukemia cases than in the control group ($p<0.0001$ and $p<0.0001$, respectively). selenium level for new case was 35.46 ± 10.93 µg/l and for patients receiving treatment was 48.12 ± 18.97 µg/l, and 83.12 ± 28.79 µg/l in healthy children. This study shows that selenium plays an important role in the pathogenesis of leukemia (ALL).

Keywords: Selenium; Antioxidant Leukemia; Atomic Absorption Spectrometry

Introduction

Selenium (Se) is an essential trace element having considerable and particular functions for human health because it is genetically encoded for which incorporation into proteins, as the constitutive part of selenocysteine, the 21st amino acid [1]. Most se-proteins have been shown to have a wide range of pleiotropic effects, ranging from antioxidant to anti-inflammatory effects [2], particularly the families of glutathione peroxidases (GPxs) and thioredoxin reductases (TrxRs) [1], but their precise mechanism is not understood absolutely currently. Despite the scarce knowledge of mechanism, a large number of laboratory and ecologic researches focused on the associations between selenium and human health have been completed [3], showing that Se is associated with several human diseases including cardiovascular disease [4,5], central nervous system disease [6], diabetes mellitus [7-10], but the results are inconsistent.

We can see worldwide debates on the relation between selenium and cancer risk. Observational studies and ran-

domized controlled trials suggest different effects in human. A new meta-analysis [11] published in Cochrane 2014 described the association between selenium and cancer prevention, and this article tended to analyze the effect of selenium supplement based on random controlled trials. There are other similar meta-analyses have been published, few of them established dose-response or beneficial range of selenium exposure associated with the risk reduction or determined the shape of dose-response curve to find whether it is a linear relation, saturation or U-shaped curve relation between selenium exposure level and cancer risk. On the other hand, numerous new studies have been reported in recent years, and we think it is meaningful to conduct an updated meta-analysis including different types of cancer to provide comprehensive evidence and clarify the shape of dose-response association between selenium status and cancer risk.

Leukemia is a group of neoplastic disorders in cells in bone marrow and blood. Leukemia is one of the most frequently observed types of cancer in children in the world. The main concern in Iran is the diagnosis and treatment of acute lymphoblastic leukemia (ALL) in children. There are many commonly-used methods for the determination of selenium in blood samples, including fluorometry, hydride-generation atomic absorption spectrometry (AAS), graphite furnace atomic absorption spectrometry, neutron activation analysis and X-ray fluorometry [12]. We measured selenium in blood serum by graphite furnace atomic absorption spectrometry.

Given this significant contribution of selenium in the human body the possibility exists that it could be used in the treatment of blood cancer. The action of selenium depends on the compound in which selenium is present. Batist and his group [13] have shown that selenosistin and sodium selenite have an anti-carcinogenic effect [13,14]. Cai et al. [15], have been studied to investigate the associations between selenium exposure and cancer risk. They identified 69 studies and applied meta-analysis, meta-regression and dose-response analysis to obtain available evidence. The results indicated that high selenium exposure had a protective effect on cancer risk. The results of linear and nonlinear dose-response analysis indicated that high serum/plasma selenium and toenail selenium had the efficacy on cancer prevention. However, they did not find a protective efficacy of selenium supplement. High selenium exposure may have different effects on specific types of cancer. It decreased the risk of breast cancer, lung cancer, esophageal cancer, gastric cancer, and prostate cancer, but it was not associated with colorectal cancer, bladder cancer, and skin cancer [15].

In the present study, we studied the serum concentration of Se, with different types of leukemia patients. Our investigation shows that there are grounds for further study of the use of special selenium compounds both for treatment as well as for preventive measures.

Materials and Methods

Patients and Controls

This study included 30 children (18 boys and 12 girls, mean age 2.6 ± 1.7 years) who had leukemia (ALL) with any prior treatment. Another 30 children (15 boys and 15 girls, mean age 2.3 ± 1.9 years) who had receiving treatment, and patients completely cured after chemotherapy (18 boys and 12 girls, mean age 2.6 ± 1.7 years) as the control group. All these children had normal neurological examination. The donors belong to a middle socioeconomic status with urban dietary habits. Informed and written consent of the parents of the cases and controls was obtained and the study protocol was approved by the ethics committee of the hospital.

Sample Collection and Treatment

The sampling of blood was performed in the Department of Pediatrics of Motahari of Urmia Hospital. Blood samples were taken at 8-9 am after fasting and collected into polypropylene tubes containing lithium heparin (Vacuette, Geiner Labortechnik, Kremsmünter, Austria). Serum was separated within 2 h, and aliquots were kept frozen at–30° C until trace element analysis. All laboratory wares including pipette tips and auto sampler cups were cleaned thoroughly with detergent and tap water, rinsed with distilled water, soaked in dilute nitric acid, and then rinsed

thoroughly with deionized distilled water.

Determination of Antioxidants in Serum

The selenium was determined by the graphite furnace atomic absorption spectrometry (AAS; SpectrAA 220, GTA 110, Varian, Australia) equipped with pyrolytically coated graphite tubes and deuterium background correction. The samples were diluted 1+4 *v*/*v* with 0.1% *v*/*v* Triton X-100. A mixture of Ni+Mg$(NO_3)_2$ was used as matrix modifier in graphite furnace AAS (GFAAS) addition to an appropriate furnace program (pyrolysis temperature of 900° C and an atomization temperature 2,600° C). This chemical modifier is proposed as the best choice among the examined modifiers for determination of selenium in serum [16].

The serum samples were diluted five times with chloric acid (0.1 N) for selenium measurements. Determination of this element was performed on a flame atomic absorption spectrometer (SpectrAA 220, Varian, Australia) equipped with deuterium background correction. The corresponding hollow cathode lamps were used as light sources with each instrument operated under the optimized conditions indicated in Tables 1,2.

The accuracy of the measurement was evaluated based on recovery studies and analysis of quality control material (Seronorm™ Trace Elements Whole Blood, Level 1, Art. No. 201405, Norway). It was supplied freeze-dried and reconstituted by adding 3 ml of water. Accuracy was 97.5% for selenium.

Statistics

Summary statistics (n, mean and standard deviation) were calculated. The changes between control and patient groups were analyzed using one-way analysis of variance (ANOVA). In addition, the other values were compared using ANOVA, taking into account sex as a grouping variable. A probability level of 0.05 or less was considered significant. Statistical evaluation was carried out by using the SPSS 11.5 for Windows.

Results

Serum antioxidant concentrations for the total subject are presented in Table 3. A significant difference in selenium levels was observed between leukemia patients (new case), patients with receiving treatment, and healthy participants as the control group ($p<0.0001$, $p<0.0001$, and $p<0.0001$, respectively). Selenium level for new case was 35.46 ± 10.93 µg/l and for patients receiving treatment was 48.12 ± 18.97 µg/l, and 83.12 ± 28.79 µg/l in healthy children (patients completely cured) respectively. In our study the healthy children mean selenium concentration in serum patients completely was cured. 102.38 ± 19.25 µg/L. Table 5 shows that serum selenium level in Iranian children is not much higher than other countries ignoring age. However, the Selenium level in children blood serum in Iran is not meaningfully different from other reported values in other countries. In this case the number of samples were 30 that is quite enough for this type of measurements, and Selenium level in our control group is same as values of human serum in other studies (Table 4). Even though the regression calculations showed a gradual decrease in the selenium level with age but the change was not significant (Figure 1). We also could not detect any significant difference in the amount of serum selenium in boys and girls (Tables 1-4).

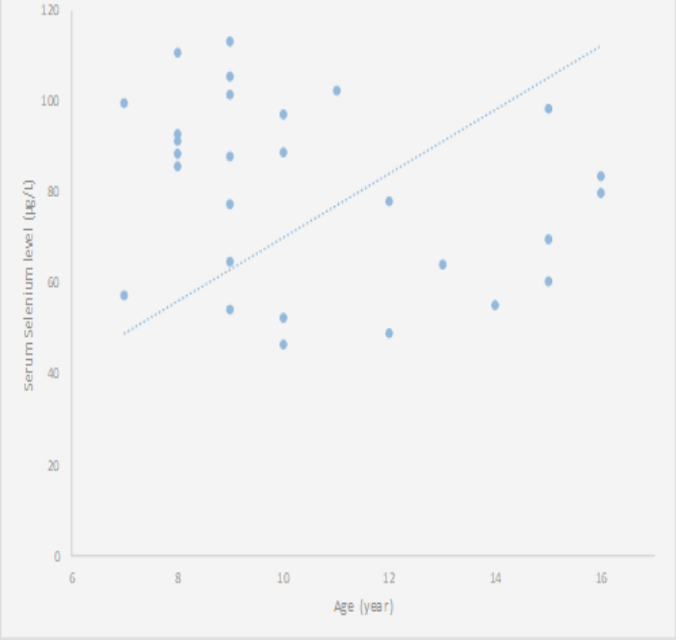

Figure 1: Relationship between serum selenium level and age in healthy children.

Table 1: Optimized Instrument Parameters and Working Conditions for Selenium Analysis in Human Serum (Instrument Settings for Determining of Selenium in Serum by GFAAS.).

Calibration mode	Measurement mode	Wavelength (nm)	Slit width (nm)	Lamp current (mA)	Sample volume (µl)	Modifier volume (µl)
Concentration	Peak height	196	1	10	10	5

Table 2: Optimized Instrument Parameters and Working Conditions for Selenium Analysis in Human Serum (Furnace Optimized Parameters for Analysis of Selenium in Serum by GFAAS.).

Element	Step	Temperature (°C)	Time (s)	Argon flow rate (l/min)
Se	Drying	85	5.0	3
	Pre last drying	95	40.0	3
	Post last drying	120	10.0	3
	Ashing	900	5.0	3
	Ashing	900	1.0	3
	Gas stop	900	2.0	0
	Ramp stop	2,600	0.8	0
	Atomization	2,600	2.0	0
	Tube clean	2,800	2.0	3

Table 3: Mean Serum of Se, Concentrations and SD* in Patients with Leukemia.

Element	new case (n=30)	with receiving treatment (n=30)	the control group	Significance of difference (*p* value)
Selenium (µg/l)	35.46 ± 10.93	48.12 ± 18.97	83.12 ± 28.79	<0.0001

Table 4: Serum selenium level according to sex in different types (mean in µg/l).

Sex	new case	patients receiving treatment	control group
girls	31.08	46.40	78.07

Table 5: Reference values of human serum selenium in different countries.

Se (µg/l)	Number of samples	Year	Location	Ref.
102 ± 28	60	1991	Iran	24
102 ± 19	30	1999	Iran	20
84.3 ± 11	54	2005	Iran	25
58.0	45	2006	Poland	26
54.3	50	1984	Finland	27
97 ± 4	987	1987	Belgium	28
82.91 ± 24.5	71	1988	France	29
115 ± 30	90	1985	Canada	30
114-177	-	1988	South Africa	31
126.4 ± 3.1	164	1987	Netherlands	32
56.2 ± 8.5	174	1994	Slovak	33
85.75 ± 22.26	130	2013	Algeria*	34
61.0 ± 13.6	292	2008	Vietnam	35
72.71 ± 1.28	61	2006	Turkey	36
108 ± 24	40	1990	China	37
101 ± 17	25	2015	Turkey	38
86.00 ± 15.00	57	2007	Iran	39
78.3 ± 18	80	2014	Egypt	40
boys	38.60	53.55	83.81	

*Northeast Region of Algeria.

Conclusion

Many studies have suggested that Selenium might play critical roles in the modulation of xenobiotic metabolizing enzymes and the glutathione system in cells [17]. As an essential component of a selenocystein-containing protein, Se is involved in most aspects of cell biochemistry and function. As such, there is much potential for Se to influence the immune system [18]. Reduced serum Se levels have been reported in patients with leukemia [19-21]. In spite of intensive and extensive studies the main cause(s) of leukemia is (are) still unknown Genetic, environmental and nutritional factors are in all probability responsible for this disease [20]. It is hoped that the ever-increasing research on different aspects of the disease and administration of a variety of drugs will lead to an effective treatment of this type of blood cancer in near future. In the present study, patients with leukemia were found to have decreased serum Se levels when compared with in the children without any prior treatment, patients receiving treatment, and healthy participants as the control group. This observation could signify that individuals with a low Se status are at increased risk of developing leukemia. On the other hand, it could indicate that the presence of leukemia is responsible for a decline of serum Se. This could be due to poor nutrition in the critically ill patient, excessive concentration of Se in leukemic cells or their environment, or some unidentified mechanism similar to the effect of chronic disorders on iron metabolism [22]. All of these findings are in favor of an inverse relationship between serum Se and disease activity in leukemia.

We gained the impression that children with leukemia had significantly low serum selenium level. Selenium acts as a major antioxidant in the form of selenoproteins

to mitigate the cytotoxic effects of reactive oxygen species. Selenoproteins are important antioxidant enzymes that are essential for proper immune system function. Changes of essential elements levels might be used as markers in clinical medicine, including diagnosis and prognosis. This case-control study shows an inverse relationship between serum selenium levels and leukemia. In another study [19-21] researchers have shown that children with different type of leukemia (acute leukemia, acute lymphoid leukemia, and acute nonlymphoid leukemia) serum Se levels were lower in patients than the controls (p<0.01). We observed no significant difference in level of serum selenium in relation to age, sex, and temperature of body. However, as the potential for cancer prevention of Se has been consistently demonstrated in experimental data, it will be of great interest to see the outcome of clinical trials testing the hypothesis that improving the Se status of a population will reduce its risk of cancer [23-42].

Acknowledgment

The authors are grateful to the Amirkabir University of Technology (Tehran, Iran) for the support of this work. The authors are also grateful for the valuable help from the staffs in the department of pediatrics of Motahari of Urmia Hospital, who diligently worked throughout the sample collection.

References

1. Roman M, Jitaru P, Barbante C. Selenium biochemistry and its role for human health. Metallomics 2013; 6: 25-54.
2. Rayman MP. Selenium and human health. Lancet 2012; 379: 1256-1268.
3. Evans SO, Khairuddin PF, Jameson MB. Optimising Selenium for Modulation of Cancer Treatments. Anticancer Res 2017; 37: 6497-6509.
4. Tanguy S, Grauzam S, de Leiris J, et al. Impact of dietary selenium intake on cardiac health: Experimental approaches and human studies. Mol Nutr Food Res 2012; 56: 1106-1121.
5. Berthold HK, Michalke B, Krone W, et al. Influence of serum selenium concentrations on hypertension: The Lipid analytic cologne cross-sectional study. J Hypertens 2012; 30: 1328-1335.
6. Rees K, Hartly L, Day C, et al. Selenium supplementation for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 2013; 1: D9671.
7. Vinceti M, Solovyev N, Mandrioli J, et al. Cerebrospinal fluid of newly diagnosed amyotrophic lateral sclerosis patients exhibits abnormal levels of selenium species including elevated selenite. Neurotoxicol 2013; 38: 25-32.
8. Park K, Rimm EB, Siscovick DS, et al. Toenail selenium and incidence of type 2 diabetes in U.S. men and women. Diabetes Care 2012; 35: 1544-1551.
9. Stranges S, Sieri S, Vinceti M, et al. A prospective study of dietary selenium intake and risk of type 2 diabetes. BMC Public Health 2010; 10: 564.
10. Bleys J, Navas-Acien A, Guallar E. Serum selenium and diabetes in US adults. Diabetes Care 2007; 30: 829-834.
11. Rajpathak S, Rimm E, Morris JS, et al. Toenail selenium and cardiovascular disease in men with diabetes. J Am Coll Nutr 2005; 24: 250-256.
12. Vinceti M, Dennert G, Crespi CM, et al. Selenium for preventing cancer. Cochrane Database Syst Rev 2014; 3: D5195.
13. Koh TS. Interlaboratory Study of blood selenium determinations. J Assoc Off Anal Chern 1987; 70: 456-457.
14. Batist G. Selenium induced cytotoxicity of human leukemia cells: Interaction with reduce glutathione. Cancer Research 1986; 46: 5482-5485.
15. Xu-Rung J: Serum selenium levels in untreated children with acute lymphoblastic leukemia. J Trace Element Electrolyte Health Dis 1990; 4: 7-10.
16. Cai X, Wang C, Yu W, et al. Selenium Exposure and Cancer Risk: An Updated Meta-analysis and Meta-regression. Sci Rep 2016; 6:19213-19231.
17. Amiri M, Farzin L, Moassesi MS, et al. Serum Trace Element Levels in Febrile Convulsion. Biol Trace Elem Res

2010; 135: 38-44.

18. Johannessen JK, Gammelgaard B, Jons O, et al. Comparison of chemical modifiers for simultaneous determination of different selenium compounds in serum and urine by Zeeman-effect electrothermal atomic absorption spectrometry. J Anal At Spectr 1993; 8: 999-1004.

19. Wong HK, Riondel J, Ducros V, et al. Effects of selenium supplementation on malignant lymphoproliferative pathologies associated with OF1 mouse ageing. Anticancer Res 2001; 21: 393-402.

20. Arthur JR, McKenzie RC, et al. Selenium in the immune system. J Nutr 2003; 135: 1457-1459.

21. Beguin Y, Bours V, Delbrouck JM. Relationship of serum selenium levels to tumor activity in acute non-lymphocytic leukemia. Carcinogenesis 1989; 10: 2089-2091.

22. Pazirandeh A, Assadi NM, Vossogh P. Determination of selenium in blood serum of children with acute leukemia and effect of chemotherapy on serum selenium level. J Trace Elements Med Biol 1999; 13: 242-246.

23. Zuo XL, Chen JM, Zhou X, et al. Levels of selenium, zinc, copper, and antioxidant enzyme activity in patients with leukemia. Biological Trace Element Research 2006; 114: 41-53.

24. Lee GR: The anemia of chronic disease. Sent Hematol 1983; 20: 61-80.

25. Clark LC, Combs GF. Selenium compounds and the prevention of cancer: research needs and public health implications. J Nutrition 1986; 116: 170-173.

26. Taherian AA. Measurement of Se, Hg, Cr, Sb, Zn, Co, and Rb in serum of staff of industrial electrolysis factories using neutron activation analysis, M.Sc. thesis, Faculty of Medical Science, Medical Science University of Tehran 1991.

27. Safaralizadeh R, Kardar GA, Pourpak Z, et al. Serum concentration of Selenium in healthy individuals living in Tehran. Nutrition J 2005; 4: 32- 39.

28. Kłapcińska B, Poprzęcki S, Danch A. Blood Selenium Concentration of Residents of Upper Silesia: Relation to Age and Gender. Polish J of Environ Stud 2006; 15: 753-758.

29. Salonen JT, Alfthan G, Huttunen JK, et al. Association between serum selenium and the risk of cancer. Am J Epidemiol 1984; 120: 342-349.

30. Begiun Y. Observation of serum trace elements in chronic lymphocytic leukemia. Cancer 1987; 60: 1842-1846.

31. Malvy JMD. Selenium and cancer in children (preliminary data) Selenium in Medicine and Biology, Walter deGruyter, Berlin 1988.

32. Gibson RS, Martinez OB, Mcdonald AC. The zinc, copper, and selenium status of a selected samples of Canadian elderly women. J Geronotol 1985; 40: 296-302.

33. Jakiewwicz K. Selenium and other mineral elements in pop Ulations at risk for esophageal cancer. Cancer 1998; 62: 2635-2639.

34. Kok EJ. Is serum selenium a risk factor for cancer in men only? Am J Epidemoil 1987; 125: 12-16.

35. Madaric A, Kadrabova J, Ginter E. Selenium concentration in plasma and erythrocytes in a healthy Slovak population. J Trace Elem Electrolytes Health Dis 1994; 8: 43-47.

36. Nait Merzoug A, Merazig H, Houam L. Determination of selenium levels in foods and plasma in a northeast region of Algeria. Food Sci Technol Lett 2013; 4: 36-40.

37. Van Nhien N, Khan NC, Yabutani T, et al. Relationship of low serum selenium to anemia among primary school children living in rural Vietnam. J Nutri Sci Vitaminol 2008; 54: 454-459.

38. Kocabas CN, Adalioglu G, Coskun T, et al. The Relationship between serum selenium levels and frequent wheeze in children. The Turkish J Pediatrics 2006; 48: 308-312.

39. Mikac-Devic M, Ference D, Tiefenbach A. Serum selenium levels in untreated children with acute lymphoblastic leukemia. J Trace Elements Electrolytes in Health

and Disease 1990; 4: 7-10.

40. Karaman S, Mansuroglu B, Kizilbey K, et al. Selenium status in blood, urine, and hair samples of newly diagnosed pediatric cancer patients. Turkish J Med Sci 2015; 45: 329-334.

41. Ashrafi MR, Shams S, Nouri M, et al. A probable causative factor for an old problem: selenium and glutathione peroxidase appear to play important roles in epilepsy pathogenesis. Epilepsia 2007; 48: 1750-1755.

42. Azab SFA, Saleh SH, Elsaeed WF, et al. Serum trace ele-

ments in obese Egyptian children: a case–control study. Italian J Pediatrics 2014; 40: 20-29.