Serum Zinc Values in Adult Patients Undergoing Bone Marrow Transplantation

Hadjibabaie M,[1] Iravani M,[2] Shamshiri AR,[3] Zaker Z,[1] Mousavi A,[2] Alimoghaddam K,[2] Kalantar E,[4] Mojtahedzadeh M,[1] Ghavamzadeh A[2]

[1]Clinical Pharmacology Department, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, IRAN
[2]Hematology- Oncology and Stem Cell Transplantation Research Center, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran
[3]Epidemiology and Biostatistics Department, Faculty of Public Health and Institute of Public Health Research, Tehran University of Medical Sciences, Tehran, IRAN
[4]Immunology Department, Iran University of Medical Sciences, Tehran, IRAN

***Corresponding author:** Ahmad Reza Shamshiri*
Department of Epidemiology and Biostatistics, Faculty of Public Health and Institute of Public Health Research, Tehran University of Medical Sciences, Tehran, IRAN
Phone Number: +98 21 84905668
Fax Number: +98 21 88004140
Email addresses: shamshiri@razi.tums.ac.ir
ar_shamshiri@yahoo.com

Abstract

Introduction: Zinc (Zn) deficiency can cause significant defects in cellular immunity. Hematopoietic stem cell transplantation (HSCT) patients usually experience serious deficiencies of all components of the immune system. Therefore, the maintenance of a normal Zn status may be important in this group of patients.
Patients and Methods: Serum Zn levels were analyzed in 55 patients during the HSCT period. As Zn-related factors, serum copper (Cu) levels and alkaline phosphatase (ALP) activity were also measured.
Results: There was decrease in Zn values immediate post-transplant period (at day +10) when compared to pre-HSCT levels (P=0.06). In patients who developed hypozincemia, adverse events appeared to occur more frequently.
Conclusion: This study suggests that maintaining a normal Zn status can be important in HSCT patients and Zn deficiency may be a risk factor causing adverse effects.
Key words: Zinc, Copper, Trace Elements, Micronutrients, Hematologic Neoplasms, Stem Cell Transplantation.

Received: 19, May, 2009
Accepted: 20, Sep., 2009

Introduction

Hematopoietic stem cell transplantation (HSCT) is a therapeutic procedure consisting of the administration of high-dose chemotherapy followed by intravenous infusion of hematopoietic stem cells to re-establish marrow function in patients with damaged or defective marrow. Although a certain amount of trace elements are supplied with plasma infusions, malabsorption and an increased need for bone marrow reconstitution may induce trace element deficiency in some patients.(1) In particular, zinc deficiency was shown to correlate with mortality after HSCT.(2) Zn deficiency in HSCT patients has attributed to low intake, TPN administration, malabsorption and increased losses from the gastrointestinal tract.(1, 3) It has been indicated that Zn requirement is increased during new hematopoiesis and also during inflammatory conditions, preventing vascular endothelial injury.(4, 5) Therefore, maintaining an optimal Zn status may be important for HSCT patients. In the present study, serum Zn levels were analyzed in adult patients undergoing HSCT. Serum copper (Cu) values and alkaline phosphatase (ALP) activity were also evaluated.

Patients and Methods

Fifty-five adult patients with malignant and non-malignant diseases who underwent allogeneic HSCT in the Hematology- Oncology and Stem Cell

Transplantation Research Center at Shariati Hospital in Tehran, Iran from May to December 2006 were prospectively evaluated for serum Zn,

Table 1. Patients' characteristics

Median age (years)	26 (rang: 14-55)
Sex	
Male	32 (58.2%)
Female	23 (41.8%)
Hematologic diseases	
AML	19 (34.5%)
ALL	15 (27.3%)
CML	7 (12.7%)
AA	5 (9.1%)
Lymphoma	5 (9.1%)
Others	4 (7.3%)

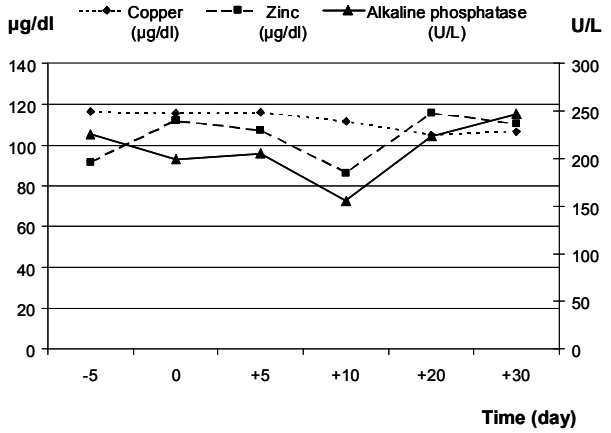

Figure 1. Trend of serum zinc, copper and alkaline phosphatase changes at different time points during HSCT

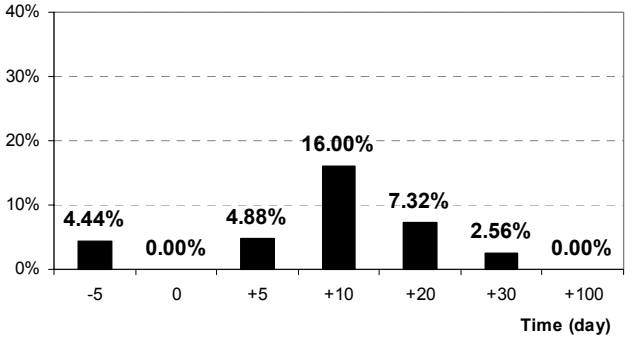

Figure 2. Percentage of patients with serum zinc deficiency during HSCT. Normal range for males were 72-127 µg/dl and for females were 70-114 µg/dl

Cu, and ALP activity at different time points: pretransplant (-5) and 0, +5, +10, +30 days after HSCT. The patients' characteristics are shown in Table 1. All patients received a pretransplant conditioning regimen including busulphan/cyclophosphamide (CY), CY/ATG, CY/Fludarabine, CCNU/VP16/CY or melphalan, and cytarabine/VP16/CY/melphalan. Graft versus host disease (GVHD) prophylaxis consisting of cyclosporine A and/or low dose methotrexate was given to all patients. Methylprednisolone was given to patients with uncontrolled GVHD.

Serum Zn levels were measured by the calorimetric method (Zn 2341 Randox UK), serum Cu levels by the spectrophotometry (Cecil UK, UV visible), and serum ALP activity by Spectrophotometry method (Covas-plus Roche). The laboratory reference was 70-124 µg/dl for serum Zn. Normal values for serum Cu ranged between 70 and 155 µg/dl. The reference value for serum ALP activity showed a wide range between 64 and 306 U/L.

The study protocol was approved by our local ethics committee. An informed consent was obtained from all patients.

The data were summarized as mean and standard deviation. The repeated measures analysis of variance (ANOVA) was also used to evaluate differences among micronutrient mean value levels at different time points. Bonferroni correction was performed for pair comparisons.

Results

The trend of changes in the serum levels of Zn, Cu, and ALP in the pre- and post-transplant patients are shown in Figure 1. The percentage of patients with Zn deficiency at different time periods has also been shown in Figure 2. Serum Zn levels were low (mean: 92.41 µg/dl) at day +10 when compared to pre-HSCT values (mean: 106.64 µg/dl) (P=0.06). Serum Zn levels increased afterward and were around baseline levels at day +30. Interestingly, all four patients who were Zn deficient at day +10 post-transplant experienced severe GVHD whereas only 21% of patients with normal Zn levels experienced this complication. The trend of ALP showed no significant changes (P=0.43) and there was no correlation between Zn and ALP pre- and pos-transplant periods. The trend of changes in serum Cu levels also showed no significant changes pre- and pos-transplant (P=0.63). All three patients who were Cu deficient at day +20 post transplant experienced severe mucositis, whereas 35% of patients with normal Cu levels experienced this problem.

Discussion

Zn affects several aspects of the immune system and Zn deficiency can cause significant defects in cellular immunity.(6) HSCT patients usually experience deficiencies of all components of the immune system.(7) Just a few studies have been done to determine Zn levels in patients undergoing HSCT.(1, 3, 8-10) One study showed a decrease in plasma Zn levels in the early post transplant period.(3) In the present study, the plasma serum levels were lowest at day +10 in patients following HSCT when compared to pre-HSCT levels. Even though the numbers of patients is small in this study, but interestingly transplant-related

complications appear to be more frequent among patients with low plasma Zn levels. At day +10, only 20% of patients with normal Zn levels had acute gastrointestinal GVHD whereas at the same time all the patients with low plasma Zn levels had acute gastrointestinal GVHD. Patients with low zinc levels have had more febrile episodes of longer duration.(3) Conditioning regimens in HSCT patients can destroy the skin and mucosa barriers which may be exacerbated by Zn deficiency. Zn is known to play an important role in wound healing. Besides, Zn plays a key role in maintaining the normal reproductive and intestinal biology and, therefore, in alleviating long-term adverse effects in HSCT patients.(5, 11) In one study that was performed on pediatric HSCT patients, there had been found a significant decrease in plasma Zn levels during the immediate post-transplant period when compared to pre-HSCT levels.(10) ALP as a Zn metalloenzyme can be an early indicator of Zn depletion.(3) In the present study, post-HSCT ALP activity was relatively higher than the pre-HSCT value. This could be attributed to GVHD, hepatitis and drug induced hepatotoxicity in some patients. Cu is another trace element that has been evaluated in this study. It has been shown that serum Cu levels negatively correlate with serum Zn levels.(11) In the present study, no significant changes in Cu levels were found during the HSCT period. Interestingly, the time of engraftment for only two patients who were Cu deficient pre-HSCT was 16 days as compared to the patients with normal Cu levels which was almost 13 days. This can suggest that normal levels of Cu are necessary for early engraftment, even though a larger population study is needed to confirm this. In another study, serum Cu levels showed no significant changes during the HSCT period in pediatric patients.(10)

Considering the complications of HSCT patients for whom intensive chemotherapy agents, antibiotics, and immunosuppressives are routinely used and therefore suffer from toxicity, infections, bleeding, and GVHD, evaluation of the Zn deficiency can be difficult. The present study can suggest that Zn deficiency in HSCT patients can be a risk factor for adverse events and maintenance of normal Zn levels can be useful for the outcome of the HSCT patients.

Acknowledgements

This research was supported by a grant from the Hematology- Oncology and Bone Marrow Transplantation Research Center, Tehran university of Medical Sciences.

References

1. Antila HM, Salo MS, Kirvela O, et al. Serum Trace Element Concentration and Iron Metabolism in Allogeneic Bone Marrow Transplant Recipients. Ann Med 1992; 24:55-59.

2. Herrmann VM, Petruska PJ. Marrow Transplant Recipients. Nutr Clin Pract 1993; 8:19-27.

3. Papadopoulou A, Nathavitharana K, Williams MD, et al. Diagnosis and Clinical Association of Zinc Depletion Following Bone Marrow Transplantation. Arch Dis Child 1996; 74:328-331.

4. Meerarani P, Ramadass P, Toborek M, et al. Zinc Protects Against Apoptosis of Endothelial Cells Induced by Linoleic Acid and Tumor Necrosis Factor Alpha. Am J Clin Nutr 2000; 71:81-87.

5. Prasad AS. Effects of Zinc Deficiency on Immune Functions. J Trace Element Exp Med 2000; 13:1-20.

6. Shankar AH, Parsad AS. Zinc and Immune Function: The Biological Basis of Altered Resistance to Infection. Am J Clin Nutr 1998; 68:447S-463S.

7. Parkman R, Weinberg K. Immunological Reconstitution Following Hematopoietic Stem Cell Transplant. In: Thomas ED, Blume KG, Forman SJ, eds. Hematopoietic Cell Transplantation, 2nd ed. Oxford, UK: Blackwell Science, 1999; 704-735.

8. Papadopoulou A, MacDonald A, Williams MD, et al. Enteral Nutrition after Bone Marrow Transplantation. Arch Dis Child 1997; 77:131-136.

9. Papadopoulou A, Williams MD, Darbyshire PJ, et al. Nutritional Support in Children Undergoing Bone Marrow Transplantation. Clin Nutr 1998; 17:57-63.

10. Uckkan D, Cetin M, Dincer N, et al. Serum Zinc and Alkaline Phosphatatse Values in Pediatric Bone Marrow Transplantation Patients. Pediatr Hematol Oncol 2003; 20:265-271.

11. Chan S, Gerson B, Subramanniam S. The Role of Cupper, Molybdenum, Selenium and Zinc in Nutrition and Health. Clin lab Med 1998; 18:673-685.