*Iranian J Publ Health, 2007, A supplementary issue on Osteoporosis, pp.30-36*

# Serum Zinc Concentration Could Predict Bone Mineral Density and Protect Osteoporosis in Healthy Men

*E Mir [1], A Hossein-nezhad [1], A Bahrami [2], MR Bekheirnia [1], E Javadi [1], A Afshar Naderi [3], *B Larijani [1]*

[1]*Endocrinology & Metabolism Research Center, Medical Sciences /University of Tehran, Tehran, Iran*
[2] *Dept. of Endocrine, Tabriz University of Medical Sciences, Iran*
[3] *Medical Biochemistry Lab. Tarbiat Modares University, Iran*

## Abstract

**Background:** A growing body of investigations demonstrated the essence role of zinc on growing and maintaining bone tissue .The idea that zinc could enhance bone content and adjourn or prevent osteoporosis in men, has been experimented as a hypothesis.

**Methods:** Six hundred healthy men (age 20-69 yr) through Iranian Multicenter Osteoporosis Study (IMOS) which is a national project running in 5 provinces in Iran for prevention and treatment of osteoporosis was selected via a cluster random sampling and enrolled the study. Bone Mineral Density was measured by biphotonic absorptimetry DEXA for hip and lumbar spine. Zinc morning serum concentration was determined by atomic absorption spectrometry. SPSS 11.5 was used for data analysis. Body Mass Index (BMI) has been calculated by Weight (kg)/Height (meter)$^2$ for each person

**Results:** The mean age was 40.83±15.06 yr .Mean BMI was 24.79±3.94 kg/m2, overlay 27.3% were smoking, 12.5% had regular physical activities three times a week and 12.2% had a history of renal stone. Among them 30.1% had zinc depletion, 56.8% normal range and 13.1% had serum zinc excess. 57.1% of individuals over 40 yr with hip osteoporosis were zinc deficient whereas 22.1% of them with normal BMD had this deficiency ($P< 0.001$).

**Conclusion:** It is concluded that zinc has a positive association with BMD in men over 40 yr and zinc deficiency is more common in osteoporotic individuals.

**Keywords:** *Zinc, Osteoporosis, Bone mineral density*

## Introduction

Osteoporosis and osteoporosis-related fractures are usually considered conditions of postmenopausal or elderly women, but these problems also occur in men. In fact, nearly 30 percent of hip fractures occur in men (1). It is estimated that the lifetime risk of experiencing an osteoporotic fracture in men over the age of 50 is 16% similar to the life time risk of developing prostate cancer (2). As in women, the mortality rate in men after hip fracture increases with age and is highest in the year after a fracture (3, 4). Over the first 6 mo, the mortality rate in men approximately doubled that in similarly aged women (5). The World Health Organization has defined osteoporosis as a bone mineral density (BMD) at the hip or spine that is ≥2.5 SDs below the mean value for young women, and osteopenia as a BMD between 1 and 2.5 SDs below these values (6). These criteria may be also applicable in men. (7, 8). Osteoporotic bones are fragile and thus prone to fractures. The condition is usually nutritional in origin and due to complicated nutrient imbalance like starvation and mineral and trace element deficiencies (9). The fact that the organic matrix in bone is mainly composed of protein and the most of the bone mineral content is calcium suggests that the important nutrients for bone health are protein and calcium (10). A significant positive correlation between human bone zinc content and bone strength suggests that zinc may play a role in

***Corresponding author**: Tel: +98 21 88026902-3, Fax: +98 21 88029399, E-mail: emrc@sina.tums.ac.ir

bone health (11). Zinc is a constituent of about 300 enzymes and Zn ions are located in the catalytic site as well as in the structural site of the enzyme complex (12, 13). Zn inhibits the differentiation of osteoclasts and promotes osteoblast activity affecting the formation of hard tissues (14). It could also increase bone growth factors and bone matrix protein which are involved in the stimulation of bone formation and cell proliferation in osteoblastic cells (15). The participation of trace elements in normal development and maintenance of the skeleton is related to their catalytic functions in organic bone matrix synthesis. Zinc regulates secretion of calcitonin from the thyroid gland and has an influence on bone turn over and can modulate hormonal effect on bone formation and calcification in bone tissue culture (15, 16).

A significant positive correlation between human bone zinc content and bone strength suggests that zinc may play a role in bone health (17). Low zinc intake has been reported to be associated with low bone mass in women (18, 19). Furthermore, reduced serum or plasma zinc concentrations and increased urinary zinc excretion have also been reported in women with osteoporosis (20-23).

However, to our knowledge, little research on the association between zinc status and osteoporosis in men has been conducted. The epidemiologic studies reported a higher fracture risk in men with low zinc intake than in men with higher zinc intake (24).

The purpose of the present study was to evaluate the independent association between serum zinc concentration and its associations with BMD through a cross sectional study.

## Materials and Methods

MOS is a large scale study has begun in 2000 in five large cities of Iran; Tehran, Mashad, Shiraz, Tabriz and Boushehr.

This project was performed by Endocrinology and Metabolism Research Center (EMRC) Tehran University of Medical Sciences, Center for Disease Control of Iranian Ministry of Health and Deputy for Health of Tehran, Mashhad, Shiraz, Tabriz and Boushehr Universites of Medical Sciences.

The original subjects (n= 6000, healthy, aged 20-69 yr) were selected as a cluster sample in the five cities with the main aim of determining the normal value of osteodensitometric variables as reference value to analyze BMD report for evaluating osteoporosis and also to determine the prevalence of osteoporosis and osteopenia in normal Iranian population. As a whole this grand study conducted to measure and to evaluate all aspects of osteoporosis and risk factors in Iran. Six hundred healthy surviving selected men aged 20-69 yr from the original IMOS study invited to participate. The subjects completed standard questionnaires concerning smoking, alcohol use, physical activity, medication use and disease history. The height and weight of the participants were measured while they wore light clothing but no shoes and body mass index (BMI; in $kg/m^2$) was calculated. BMD was measured at the trochanter, intertrochanter, femoral neck, Ward's triangle and lumbar spine by using dual X-ray absorbtiometry (Lunar Corp, Madison, WI).Instruments were calibrated daily and had measurement precisions of $\leq$ 1% for the spine, $\leq$ 1.5% for the hip. Total hip BMD was obtained by summing the bone mineral content values at the femoral neck, intertrochanter and greater trochanter and dividing this value by the composite area of the three sites. Spine BMD was defined as the average BMD of lumbar vertebrae $L_2$-$L_4$.Osteoporosis for all axial sites was defined as $T_{score} \leq -2.5$ and osteopenia was defined as a $T_{score}$ between -1 and -2.5 (6).

After the subjects had fasted overnight, blood samples were drawn into trace mineral-free plastic tubes each containing 2 drops of 2% sodium oxalate and were placed on ice. The blood was centrifuged within 2 h at 3000 x *g* for 10 min to obtain serum. Serum samples frozen at -70 °C were shipped on dry ice to the Mineral Analysis Laboratory at the Tarbiat Modaress University Biochemistry Lab. Serum zinc concentrations were measured by using an induction coupled serum

atomic emission spectrometer. Normal range of serum zinc concentration considered 75-120 µg/dl according to the second National Health and Nutrition Examination Survey (NHANES) of the United States (1976-80). They were divided to two age groups (age: 20-40, 302/600) and (age: 40-75, 288/600) for more simplicity and accuracy of results. All process has been confirmed by Tehran University of Medical Sciences Medical Ethics Committee.

SPSS version 11.5 was used for data analysis. Student *t*-test was used to compare means. Pearson's coefficients were calculated to evaluate the correlation of serum zinc concentrations with age, BMI and BMD. Mean age, BMI and serum zinc concentration was compared between the two age groups with osteoporosis, osteopenia, or normal BMD. The strength of association between the BMD and serum zinc concentration was measured by linear regression model. As BMD was significantly associated with age and BMI, serum zinc concentrations were compared after adjustment for these two major confounders. The proportions of men who smoked cigarettes or exercised regularly were compared between the 2 groups using a chi-square test.

## Results

The baseline characteristics of the subjects are shown in Table 1. The mean age was 40.83± 15.06 y (range: 20-69 yr). The mean BMI was 24.79±3.94 kg/m$^2$, overall, 27.3% of the subjects were current smokers, and 12.5% reported that they exercised 3 times /wk and 12.2% had a history of renal stone. Overall mean serum zinc concentration was defined 92.15±35.15 µg/dl. Among them 30.1% had zinc depletion, 56.8% in normal range and 13.1% had serum zinc excess. BMD values for hip was significantly lower in the men over 40 in the lowest quartile of serum zinc concentration (<75 µg/dl) than in the men with higher serum zinc ($P$< 0.05). This amount was not significant for spine either (Table 2). Individuals over 40 with hip osteoporosis had a mean zinc serum concentration about 72.15± 16.9 µg/dl while in whom with normal BMD this amount was 98.84±35.6 ($P$< 0.001) (Table 2). It should be clarified that these correlations were not observed in under 40 yr age group. There was no significant difference in serum vitamin D level among zinc deficient and normal zinc individuals totally. After adjustment for confounders such as age and BMI the only significant association that remained was between serum zinc and total hip BMD ($P$= 0.029) (Fig.1).

**Table 1:** Baseline characteristics of the subject

| **Characteristic** | |
|---|---|
| **Anthropometric variables (n=600)** | **Value** |
| Age (yr) | 40.83±15.06[1] |
| BMI (kg/ m$^2$) | 24.79±3.94 |
| BMD Total (gr/cm$^2$) | 1.02±0.16 |
| BMD Spine (gr/cm$^2$) | 1.14±0.16 |
| Current smoker % | 27.3 |
| Exercise 3 times/week % | 12.5 |
| Renal stone% | 12.2 |
| Serum zinc concentration (n=600) (µg/dl) | 92.15±35.15 |

[1]±SD (all such values)

**Table 2:** Correlations of serum zinc concentration with age, BMI, Hip BMD, Spine BMD and WHR in men <40 yr and men >40 yr

| | **<40** | | **>40** | |
|---|---|---|---|---|
| | **Correlation coefficient** | ***p*** | **Correlation coefficient** | ***p*** |
| Age | 0.023 | 0.70 | -0.17 | 0.003 |
| BMI | 0.108 | 0.70 | 0.14 | 0.015 |
| WHR | 0.086 | 0.15 | -0.09 | 0.13 |
| BMD (Total Hip) | 0.015 | 0.81 | 0.17 | 0.003 |
| BMD (Spine) | -0.002 | 0.97 | 0.091 | 0.12 |

| Cross sectional characteristics depending on zinc status in men>40 | | | |
|---|---|---|---|
| | NL zinc concentration | zinc deficient | *P* |
| Age yr | 53.1±9.1 | 55.6±8.5 | 0.03 |
| BMD gr/cm$^2$ (Total Hip) | 0.98±0.14 | 0.92±0.14 | 0.00 1 |
| BMD (Spine) | 1.07±0.16 | 1.10±0.15 | 0.12 |

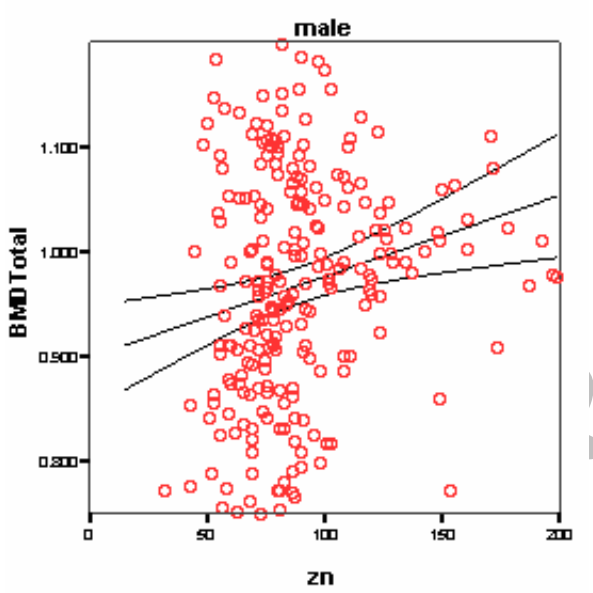


**Fig. 1:** Association of serum zinc concentration with Total hip BMD in men

## Discussion

It is well known that zinc is essential for the growth of human and other animals. Zn is involved in the stimulation of bone formation by osteoblasts and inhibition of bone resorption by osteoclasts (25, 26). Evidences suggest that zinc deficiency is one of the important problems within the developed and developing countries (27). Zinc deficiency in human was reported for the first time in Iran in 1961 and in Egypt in 1963 (28). Following studies on junior high school children highlighted a high prevalence of zinc deficiency in our population (29, 30). Infants, children in growing age, pregnant and breast feeding women, individuals over 50, alcoholics and vegetarians are at the risk of zinc deficiency more often (31-34). This study is the first ever in Iran has investigated serum zinc content in elderly men and its association with osteoporosis .The serum zinc was measured as the growing body of evidences suggest its significance for indicating population's zinc status, however it is not considered to be a reliable indicator of zinc status in individual persons (35-37). The serum zinc has been shown a higher concentration in morning samples than in afternoon or evening samples (32), so all blood samples were taken fast morning. The measurements were based on the cut-off recommended by NHNAES (33) and illustrated about one third of our male population over 40 are zinc deficient.

In the present study the mean serum zinc concentration for all subjects was 92.15±35.15 µg/dl which was similar to the result from NHANES II in 1976-1980 (33) an epidemiologic survey conducted in Rome (34) and Ranch Bernardo Study (31). Our study illustrated measured serum zinc concentrations were significantly lower in men with hip osteoporosis than in men without osteoporosis. BMD values for total hip were significantly lower in men in the lowest quartile of serum zinc concentration (<75 µg/dl) than in men with higher serum zinc concentration. These amounts were not significant for spine. Other investigations have reported significant correlation for hip and spine too (31).

Serum zinc concentration correlated with age and was not correlated with BMI. Other researches have reported no significant correlation of serum zinc with age (35-38) or BMI (36) but similar result showing association between blood zinc and age (33, 34, 39, 40) and negative association with BMI (40) have also been reported.

Regarding the great burden of this debilitative disease especially in men in Iran and besides our finding of a huge number of men with zinc deficiency, this study tries to focus on the beyond effect of an trace element such as zinc on bone strength. Considering the paucity of researches conducted on male osteoporosis and

its mysterious etiology, this investigation could unveil one of the nutritional facts concerning zinc and bone content. Of course if we could provide FFQ and recall records for monitoring zinc consumption and consider daily intake parallel to measuring serum zinc concentration it would be more practical in recommending preventive issues to public health.

The study concluded that zinc had a positive association with BMD in men over 40 and zinc deficiency was more common in osteoporotic indi-viduals. It seems that inserting corrected eating habits, modifying life style, wide spreading the knowledge of nutrients and approved medical recommendation to the society would lead to building strong and healthy bones and would result in the prevention of bone injury and decrease the burden of this debilitative disease.

## Acknowledgements

I would like to extend my sincere appreciation to my colleagues' cooperation in Osteoporosis team for accomplishing the manuscript. The research project has been totally granted by EMRC.

## References

1. Campion JM, Maricic MJ (2003). Osteoporosis in men. *Am Fam Physician*, 67(7): 1521-26.
2. Melton LJ, Chrischilles EA, Cooper C, et al. (1992). Perspective. How many women have osteoporosis? *J Bone Miner Res,* 7(9): 1005.
3. Merrill RM, Weed DL and Feuer EJ (1997). The lifetime risk of developing prostate cancer in white and black men. *Cancer Epidemiol Biomarkers Prev*, 6(10):763-68.
4. Kanis JA, Oden A, Johnell O, et al. (2003). The components of excess mortality after hip fracture. *Bone*, 32(5): 468-.73.
5. Seeman E (1995). The dilemma of osteoporosis in men. *Am J Med,* 98 (suppl. 2A): 76S-88S.
6. Trombetti A, Herrmann F, Hoffmeyer P, et al. (2002). Survival and potential years of life lost after hip fracture in men and age-matched women. *Osteoporos Int*; 13(9): 731-7.
7. World Health Organization. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group (1994). *World Health Organ Tech Rep Ser,* 843: 1-129.
8. Kanis JA, Johnell O, Oden A, Jonsson B, De Laet C, Dawson A (2000). Risk of hip fracture according to the World Health Organization criteria for osteopenia and osteoporosis. *Bone*, 27(5): 585-90
9. Pande I, Francis RM (2001). Osteoporosis in men. *Best Pract Res Clin Rheumatol*, 15(3): 415-27.
10. Palmer N (1993). Metabolic diseases of bone. In: *Pathology of domestic animals*. Eds, KVF Jubb, PC Kennedy, N Palmer. 4th ed, Academic Press, Orlando, Florida, pp.55-93.
11. Ilich JZ, Kerstetter JE (2000). Nutrition in bone health revisited: a story beyond calcium. *J Am Coll Nutr*,19(6): 715–37
12. Alhava EM, Olkkonen H, Puittinen J, Nokso-Koivisto VM (1977). Zinc content of human cancellous bone. *Acta Orthop Scand*, 48(1): 1-4.
13. O'Dell BI (1992). Zinc plays both structural and catalytic roles in metallprpoteins. *Nutr Rev,* 50(2): 48-50
14. Murphy P, Wadiawala I, Sharland De, Rai GS (1985). Copper and Zinc level in health and sick elderly. *Am Geriatr Soc,* 33: 847-49.
15. Kishi S, Yamaguchi M (1994). Inhibitory effect of zinc compounds on osteoblast-like cell formation in mouse marrow cultures. *Biochem Pharmacol*, 48(6): 1225-30.
16. .Masayoshi Yamaguchi (1998). Role of zinc in bone formation and bone resorption.

*The Journal of Trace Elements in Experimental Medicine*, 11(2-3)119-35.
17. Palacios C (2006). The role of nutrients in bone health, from A to Z. *Crit Rev Food Sci Nutr*, 46(8): 621-8.
18. Freudenheim JL, Johnson NE, Smith EL (1986). Relationships between usual nutrient intake and bone mineral content of women 35-65 yr of age: longitudinal and cross-sectional analysis. *Am J Clin Nutr*, 44(6): 863-76.
19. Angus RM, Sambrook PN, Pocock NA, Eisman JA (1988). Dietary intake and bone mineral density. *Bone Miner*, 4(3): 26577.
20. Gur A, Colpan L, Nas K, et al. (2002). The role of trace minerals in the pathogenesis of postmenopausal osteoporosis and a new effect of calcitonin. *J Bone Miner Metab*, 20(1): 39-43.
21. Lowe NM, Fraser WD, Jackson MJ (2002). Is there a potential therapeutic value of copper and zinc for osteoporosis*? Proc Nutr Soc*, 61(2): 181-5.
22. Relea P, Revilla M, Ripoll E, Arribas I, Villa LF, Rico H (1995). Zinc, biochemical markers of nutrition, and type I osteoporosis. *Age Ageing*, 24(4): 303-7.
23. Herzberg M, Foldes J, Steinberg R, Menczel J (1990). Zinc excretion in osteoporotic women. *J Bone Miner Res*, 5(3): 251-57.
24. Elmstahl S, Gullberg B, Janzon L, Johnell O, Elmstahl B (1998). Increased incidence of fractures in middle-aged and elderly men with low intakes of phosphorus and zinc. *Osteoporos Int*, 8(4): 333-40.
25. Miller LV, Krebs NF, Hambidge KM (1998). Human Zinc Metabolism: advancesin the modeling of stable isotope data. *Adv Exp Med Biol*, 445: 253-69.
26. Halstead JA, Ronaghy HA, Abadi P, et al. (1972). Zinc defficiency in men. The Shiraz Experiment. *Am J Med*, 53: 277-84
27. Parsad AS, Miale Jr, Farid Z, Sandstead HH, Schubert AR, Darby WJ (1963). Biochemical Studies on dwarfism hypogonadism and anemia. *Arch Int Med*, 111: 407-28.
28. Mahmoodi MR, Kimiagar SM (2001). Prevalence of zinc deficiency in junior high school students of Tehran. *Biol Trace Elem Res*, l81(2): 93-103.
29. Shrifi F, Hedayati M, mirmiran P, et al. (1999). Serum level of zinc, copper and iron in the high school children of 23 provinces of Iran, *IRN J Endocrinol Metab*, 4: 275-86.
30. Ilich JZ, Kerstetter JE (2000). Nutrition in bone health revisited, a history beyond calcium. *J Am Clin Nutr*, 19(6): 715-37.
31. Taisun H Hyun, Elizabeth Barrett-Connor, David B Milne (2004). Zinc intake and plasma concentrations in men with osteoporosis: the Rancho Bernardo Study *American Journal of Clinical Nutrition*, 80(3): 715-21.
32. Menditto A, Morisi G, Alimonti A, et al. (1993). Association of serum copper and zinc with serum electrolytes and with selected risk factors for cardiovascular disease in men aged 55-75 years. NFR Study Group. *J Trace Elem Electrolytes Health Dis*, 7(4): 251-3.
33. Hotz C, Peerson JM, Brown KH (2003). Suggested lower cutoffs of serum zinc concentrations for assessing zinc status: reanaylsis of the second National Health and Nutrition Examination Survey data (1976–1980). *Am J Clin Nutr*, 78(4): 756-64.
34. Vir SC, Love AHG (1979). Zinc and copper status of the elderly. *Am J Clin Nutr*, 32(7): 1472-6.
35. Hashim Z, Woodhouse L, King JC (1996). Inter individual variation in circulating zinc concentrations among healthy adult men and women. *Int J Food Sci Nutr*, 47(5): 383-90.
36. Artacho R, Ruiz-Lopez MD, Gamez C, Puerta A, Lopez MC (1997). Serum concentration and dietary intake of Zn in

healthy institutionalized elderly subjects. *Sci Total Environ*, 205(2-3): 159-65.

37. Del Corso L, Pastine F, Protti MA, et al. (2000). Blood zinc, copper and magnesium in aging. A study in healthy home-living elderly. *Panminerva Med*, 42(4): 273-77.
38. Monget AL, Galan P, Preziosi P, et al. (1996). Micronutrient status in elderly people. Geriatrie/Min. Vit. Aux Network. *Int J Vitam Nutr Res*, 66(1): 71–6.
39. Savarino L, Granchi D, Ciapetti G, et al. (2001). Serum concentrations of zinc and selenium in elderly people: results in healthy nonagenarians/ centenarians. *Exp Gerontol*, 36(2): 327-39.
40. Di MartinoG,Matera MG,De Martino B, Vacca C, et al. (1993).Relation between zinc and obesity. *J Med*, 24:177-83.