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Effect of menopausal hormone therapy on the levels of magnesium, zinc, lead and cadmium in post-menopausal women

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Abstract

Introduction and objective: The level of trace elements is extremely important for the maintenance of normal functioning of the human body. The risk of disturbance of their balance increases especially dynamically during the period of menopause. The objective of the study was the effect of MHT on the levels of bioelements (Mg and Zn) in blood plasma, and toxic metals (Pb and Cd) in the whole blood in postmenopausal women.

Materials and methods: The study covered 323 women at postmenopausal age from the population of the West Pomeranian Region, in whom the levels of Mg, Zn, Pb and Cd were determined. The women were divided into two groups: study and control. The study group were 152 women who used menopausal hormone therapy (MHT). The control group were 171 women who did not use MHT, and had had their final menstrual period at least one year prior to inclusion in the study. The mean age of the women examined was 56±5.

Results: Significantly higher levels of the bioelements Mg, Zn were observed in women who used MHT, compared to the control group ($p<0.05$). The concentration of Pb in whole blood was significantly lower in the study than the control group: 16.09±7.33 µg/l and 20.18±9.01 µg/l, respectively. An elevated level of Cd in whole blood was found in both groups of women: 0.9±1.03 µg/l and 0.8±1.1 µg/l, respectively. It was noted that women who used MHT more frequently declared the presence of climacteric symptoms ($p<0.05$).

Conclusions: 1) Higher levels of Mg and Zn were found in blood plasma of women who used MHT. 2) The mean concentration of Cd in the blood of women in both groups was similar. 3) In women who use MHT the level of Pb in whole blood was lower, compared to the rest of the women.

Key words

bioelements, toxic metals, MHT, menopause, climacteric symptoms

INTRODUCTION

Menopausal hormone therapy (MHT) exerts an effect on the quality of life of women by reducing negative climacteric symptoms associated with hot flushes, alleviating troublesome vasomotor symptoms, improving the quality of sleep, and functioning in the sexual sphere [1]. The use by women of hormone therapy also decreases the symptoms of depression. In the opinions of 78% of respondents who used replacement therapy it allowed prevention of the development of unpleasant complaints typical of the menopausal period [2].

However, some reports indicate that this therapy may cause an increase in morbidity due to breast cancer. Also, many positive aspects of the use of hormone replacement therapy, such as a decrease in the risk of fractures and development of colon cancer, cease to exist after discontinuation of treatment [3].

Mg plays various roles in the human body, affects the stabilization of the DNA and its synthesis, maintains integrity of the mitochondrial membranes, exerts an effect on the processes of anaerobic glycolysis and oxidative phosphorylation, and in combination with Ca affects the excitability of nerve and muscle tissue, as well as muscle contractility. An insufficient level of Mg may result in the development of atherosclerotic changes and cardiovascular diseases. In addition, it was found that the level of Mg in blood serum and in hair is associated with bone mineral density in women during the premenopausal period [4].

Zn is a component of 59 metal-containing enzymes and is indispensable for the normal synthesis of lipids and nucleic acids. The concentration of Zn in human serum is from

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11.5-17.6 μmol/l (6.5-8.8 μg/l). The greatest amount of this element (over 75%) is cumulated in erythrocytes in the form of carbonic anhydrase. The main sources of Zn are food products, such as meat, fish, vegetables and cereals [5].

Mg and Zn are elements especially important for the normal functioning of women during the postmenopausal period. The deficiency of Mg and Zn in women at this age may cause or intensify the occurrence of heart palpitations, trembling of hands and feet, paresthesia, disorders in the functioning of the immune system, as well as symptoms of dryness and hardness of the skin, hair loss, apathy, depression, concentration disorders, impaired vision, taste, smell and hearing. These changes are obviously reversible after supplementation of the existing deficits [6, 7, 8].

Pb is a heavy metal exerting a toxic effect on the human body. Shortly after the penetration of Pb into the organism it is transferred via blood to the soft tissues and organs, such as the liver, kidneys, lungs, brain, spleen, muscles and heart. After several weeks, Pb cumulates in bone tissue. In adults, approximately 94% of the total Pb present in the body is deposited in bones and teeth, whereas in children – about 73%. A certain amount of Pb may be stored in bones for decades, while the remaining part may leave this reservoir and return to the blood or transfer to other organs in special situations, e.g. pregnancy, period of breastfeeding, bone fracture or advanced age [9]. To a considerable degree, Pb may contribute to the development of physiological and biochemical disorders. It has been confirmed that occupational exposure to this element may result in damage to DNA [10].

The most hazardous effect of Pb is that on the nervous system. In the case of exposure to high doses of Pb, this may seriously damage the brain and kidneys, leading even to death [9]. In pregnant women, exposure to high doses of Pb may lead to abortion [11], while in males – to disturbances in sperm production and decrease in fertility [12].

There are no confirmed data which evidences that Pb may have a carcinogenic effect on the human body. Nevertheless, in rats and mice the development of renal tumours has been noted as a result of exposure to high doses of Pb. Many organizations, such as the Department of Health and Human Services, EPA, and International Agency for Research on Cancer, consider Pb as an element potentially carcinogenic in humans.

Cd is a metal-containing toxin which negatively affects the functioning of the human organism. A long-term, many-year exposure to small doses of Cd in inhaled air may result in the in-building of this metal into the structure of the kidneys and, in consequence, diseases of this organ. The amount of 0.01 μg Cd/m^3 has been adopted as a minimum hazardous dose which affects the human body in the case of prolonged exposure lasting for more than one year. Many studies indicate the development of respiratory diseases as a consequence of prolonged exposure to Cd, the symptoms of which are dyspnea, cough, wheezing and pulmonary function disorders [13]. In 1999, the Agency for Toxic Substances and Disease Registry (ATSDR) considered Cd as one of the 7 substances present in the environment, which show an especially negative effect on human health [14]. In the total population, the consumption of food and water with high contents of Cd may cause irritation of the stomach, resulting in vomiting or diarrhea, which in some cases may result in death. The amount of 0.5 μg Cd/kg/daily has been considered as the minimum hazardous dose of Cd, supplied via the alimentary route over a medium-length of time, i.e. from 15-364 days. To-date, the lowest dose has not been determined for humans which in a shorter time (up to 14 days) would produce the symptoms of acute intoxication with Cd via the alimentary route. The consequence of such an exposure may be brittleness of bones, manifested as susceptibility to fractures. For humans, the minimum hazardous level of Cd chronically supplied (for more than 1 year) by the alimentary route has been established as 0.1 μg/kg/daily. Studies conducted on laboratory animals confirmed the presence of the relationship between exposure to Cd and the occurrence of disorders concerning the kidneys and bones. In addition, it was found that Cd causes anaemia, hepatic diseases, damage to the brain and nerves. With respect to humans, there are no clear data yet which would evidence the presence of the relationship between an elevated level of Cd and these disorders [15]. Another serious consequence of exposure to Cd is an increase in mortality due to cancerous diseases. It has been observed that lung cancer was more frequently diagnosed in employees exposed to the inhalation of Cd. These data were confirmed in laboratory studies on rats. Many organizations dealing with public health, such as the *U.S. Department of Health and Human Services* (DHHS), *International Agency for Research on Cancer* (IARC) or *Environmental Protection Agency* (EPA), have considered Cd as an identified carcinogenic factor in humans [15]. Cd may be responsible for disorders in the metabolic processes regulated by Zn, such as the synthesis of nucleic acids and lipids in cells [16].

OBJECTIVES

Evaluation of the effect of MHT on the levels of bioelements (Mg and Zn) in blood plasma, and toxic metals (Pb and Cd) in the whole blood of postmenopausal women.

MATERIAL AND METHODS

The study covered 323 women at postmenopausal age from the population of the West Pomeranian Region, who had the level of Mg and Zn in blood serum and Pb and Cd in whole blood determined. The mean age of the women in the study was 56±5.

The women were divided into two groups: study and control. The study group were 152 women who used menopausal hormonal therapy (MHT). The control group were 171 women who did not use MHT, and had had their final menstrual period at least one year prior to inclusion in the study. The women examined were healthy non-smokers who did not abuse alcohol, exercised moderate physical effort, did not apply elimination diets, and did not take any vitamins or mineral supplements. In all the respondents the values of arterial blood pressure were normal, and the presence of endocrinological disorders (thyroid gland diseases and diabetes, as well as oncologic diseases were excluded. The patients were informed about the aim of the study and expressed their written consent to participate. The study was conducted with the consent of the Bioethical Commission of the Pomeranian Medical University in Szczecin (Permission No. KB-0080/187/09 of 14 December 2009).

In order to perform the biochemical analysis of the levels of Mg, Zn, Pb and Cd, blood was drawn from the cubital vein using the vacutainer system. Blood was taken in a surgery, observing the procedures and principles related with blood collection and transportation to the laboratory.

In order to measure concentrations of Mg and Zn, 5 ml of blood were collected with the vacutainer system. The blood was centrifuged at 4,000 rpm for 10 min. and the serum harvested. Concentrations in serum were determined by flame atomic absorption spectrometry (PU 9100X, Philips, Cambridge, UK). Diluted serum samples were introduced directly into the flame. The samples were 1:80-diluted with lanthanum solution in hydrochloric acid. Analytical wavelength was 285.2 nm for Mg and 213.9 nm for Zn. Concentration values were read from the calibration curve. Internal quality control in the laboratory was performed on two levels i.e. using two types of serum, namely, serum with normal magnesium and zinc concentrations and serum with Mg and Zn concentrations below normal. The simple 2–2SD Westgard rule was used for result acceptance. This rule states that if one control measure exceeds the mean ±2SD, it is necessary to repeat the control measurement. If the result is within the expected values, then it is assumed that the previous deviation was a random incident, and the run should be accepted as 'in control'. However, if the control measure exceeds the mean ±2SD again, a systematic error is likely, and the results therefore cannot be accepted as reliable (the run should be rejected). In such circumstances, troubleshooting was performed and testing repeated. The control results were plotted on Levey–Jennings charts.

The laboratory tests were performed in the Department of Biochemistry and Chemistry at the Pomeranian Medical University in Szczecin (Poland) in accordance with the PN-EN ISO 15189 guidelines. Serum Mg concentrations between 1.87-2.4 mg/dl and Zn levels between 75-130 µg/dl were accepted as laboratory reference standards [17].

The concentrations of Pb and Cd were evaluated after collecting 5 ml of blood from the vein into one test tube using the vacutainer system. Biological material was stored at the temperature of -20°C. Blood was transported under cold conditions to the Institute of Occupational Medicine and Environmental Health at the Department of Chemical Hazards in Sosnowiec. The contents of metal-containing toxins was determined in the Laboratory for Metals Analysis. The analytical procedure was based on the Stoppler and Brandt method. The levels of Pb and Cd were evaluated in the blood specimen deproteinized with nitric acid, in the supernatant, with the use of Graphite Furnace Atomic Absorption Spectrometry (GFAAS) (also known as Electrothermal Atomic Absorption Spectrometry (ETAAS). For non-specific absorption Zeeman background correction was used. The measurement was performed with the use of a Perkin Elmer 4100ZL Atomic Absorption Spectrometer. Studies carried out in this centre are subject to regular quality control by participation in the system of the national and international quality control by the Institute of Occupational medicine in Łódź, Istituto Superiore di Sanita in Rome, and CDC in Atlanta (USA).

According to the interpretation by the Laboratory, a value lower than 100 µg/l was considered as the maximum lead concentration.

According to the guidelines by the Institute of Occupational Medicine and Environmental Health the normal level of cadmium in whole blood is 1.5 µg/l, on average.

Statistical calculations were performed with the use of Statistica PL software. The study sample was analyzed from the aspect of quantitative variables by evaluating minimum and maximum value, arithmetic mean, and standard deviation. The differences between two independent groups were analyzed by means of U Mann-Whitney test. The p values p≤0.05 were considered statistically significant.

SOCIO-DEMOGRAPHIC DATA OF WOMEN IN THE STUDY

The mean age of the women in the study group was 54.8±4.9, whereas in the control group – 56.4±5.6. The majority of women were married, both in the study and control groups: 77.0% and 67.3%, respectively. It was noted that the education level of the women examined had an effect on the use of MHT. In the group of women with an elementary and elementary vocational education level, 41.2% of respondents decided to apply this therapy, among those with secondary school education – 46.0%, while among women who had university education – 50.4%. In both groups, the majority of women were occupationally active. Respondents who applied MHT more often had normal body weight (according to the BMI) than those who did not use this type of therapy; however, the statistical difference was at the limit of significance (p≤0.05). In the case of women who were overweight and obese, no statistically significant differences were confirmed. In addition, the occurrence of climacteric symptoms, which are characteristic for the postmenopausal period, was analyzed. It was observed that women who applied MHT more often declared the lack of climacteric symptoms (p<0.05). Moreover, women who did not use MHT significantly more frequently indicated weak and strong intensification of climacteric symptoms, compared to those who applied the therapy (p<0.05 each) (Tab. 1).

Table 1. Sociodemographic data of women in the study

Variables	Study group n=152		Control group n=171		
	n	%	n	%	
Education level					
Elementary/elementary vocational	14	9.21	20	11.70	
Secondary school	80	52.63	94	54.97	
University	58	38.16	57	33.33	
Marital status					
Unmarried	35	23.03	56	32.75	
Married	117	76.97	115	67.25	
Occupational activity					
Occupationally active	107	70.39	112	65.50	
Occupationally inactive	45	29.61	59	34.50	
BMI					p
Normal weight	74	48.68	68	39.77	<0.05
Overweight	54	35,53	67	39.18	>0.05
Obesity	24	15,79	36	21.05	>0.05
Degree of intensification of climacteric symptoms according to Kupperman index					
Lack of climacteric symptoms	111	73.03	99	57.89	<0.05
Poorly intensified climacteric symptoms	15	9.87	30	17.54	<0.05
Medium-intensified climacteric symptoms	15	9.87	19	11.11	>0.05
Strongly intensified climacteric symptoms	11	7.24	23	13.45	<0.05

RESULTS

Analysis of data showed that the mean levels of Mg were lower than the standard in all women in the study, and lower levels of Zn in women who did not use MHT. It was also confirmed, that the mean levels of Mg and Zn in blood plasma of women using MHT were significantly higher, compared to those who did not apply this therapy ($p<0.05$). The mean levels of toxic metals Pb and Cd did not exceed the mean allowable values; however, the concentration of Pb in whole blood of women who used MHT was significantly lower ($p<0.05$) than in the control group (mean concentrations were 16.09±7.33 µg/l and 20.18±9.01 µg/l, respectively. No statistically significant differences in the level of Cd were observed between women in both groups ($p>0.05$) (Tab. 2, 3).

Table 2. Levels of Mg and Zn with consideration of use of MHT

Variable		n	$\bar{x} \pm SD$	Min-Max	z	p
Mg (mg/l)	Study group	152	17.07±3.45	9.19-25.65	-5.06	<0.05
	Control group	171	15.13±2.76	8.69-23.63		
Zn (mg/l)	Study group	152	0.76±0.21	0.43-1.78	-4.01	<0.05
	Control group	171	0.68±0.15	0.43-1.18		

z – U-Mann-Whitney test
p – level of significance

Table 3. Levels of Pb and Cd with consideration of use of MHT

Variable		n	$\bar{x} \pm SD$	Min-Max	z	p
Pb (µg/l)	Study group	152	16.09±7.33	4-40	4.055	<0.05
	Control group	171	20.18±9.01	3-56		
Cd (µg/l)	Study group	152	0.9±1.0	0.07-6.09	-0.22	>0.05
	Control group	171	0.8±1.1	0.13-8.65		

z – U-Mann-Whitney test
p – level of significance

DISCUSSION

The level of trace elements is of the utmost importance for the maintenance of normal functioning of the human organism. The risk of disturbance of their balance, especially dynamically, increases during the period of menopause. Studies conducted by Meram et al. showed that the use of MHT exerts a positive effect on the concentration of trace elements, including vitamins A and E [18]. Bureau et al. observed that women who applied MHT to a smaller degree than the reminder lost Mg and Zn with urine. The levels of Cu and Cr in blood serum of women treated with MHT was also higher, which allowed the conclusion that the therapy has a beneficial effect on the contents of trace elements in postmenopausal women [19]. This has been confirmed by own studies, where higher levels of Mg and Zn were also noted in women who applied menopausal hormone therapy.

Estrogens show procoagulant effects, additionally enhanced by high levels of Ca in blood, caused by a high intake of this element recommended for protection against osteoporosis during the perimenopausal period. An insufficient level of Mg, which plays an important role in contracting thrombosis and inhibiting aggregation of blood platelets, also unfavourably affects the cardiovascular system. Mg shows a protective effect on the central nervous system, thus resulting in an improvement of blood flow in cerebral vessels and stimulating its metabolism. It was confirmed that the use of hormone replacement therapy during the postmenopausal period improves the psychological functioning of women. An increase in the level of Mg in blood reduces vascular risk, and simultaneously harmonizes with MHT in order to improve the psychological state of women [20].

Studies confirm that therapy based on hypolidemic drugs, supported by Mg supplementation, brings about the most beneficial effects in the treatment of lipid disorders [6]. Studies carried out among postmenopausal women indicated that a short-term (30-day) oral supplementation of magnesium citrate at a dose of 1.830 mg /daily resulted in inhibition of bone turnover [7].

Studies carried out in a group of 3,721 women in the UK showed that among those treated with MHT the problems associated with hot flushes, night sweating, muscle and joint pain, sleeplessness and vaginal dryness occurred significantly more rarely than in the control group [21]. Own studies have confirmed a significant effect of the use of MHT on the presence of climacteric symptoms, because the women who used this therapy more frequently declared the lack of such symptoms.

Sunar et al. did not observe any statistically significant effect of ZN supplementation in small doses within the period of two weeks on the level of progesterone and estrogen in women during the period of natural menopause, although a tendency was noticed towards a directly proportional increase in the level of these hormones, according to an increase in the Zn dose [22]. Studies conducted on rats after the excision of ovaries showed that Zn deficiency resulted in a considerable decrease in the levels of Ca and P in their organisms, while the supplementation of this element prevented such complications [23].

In the human body, Pb accumulates mainly in the bones. It was confirmed that during the period of menopause, Pb accumulated in the bone skeleton penetrates into the blood to great degree [24]. It was noted that in women who experienced menopause as a result of surgery, a lower level of Pb in blood was observed than among those who experienced this process naturally. This difference is probably due to the lower mean age of patients who had undergone surgical treatment, as well as their more common use of MHT. It was found that MHT was applied by 87% of respondents who experience menopause as a result of surgery, while by only 58% of those in whom menopause occurred naturally [25].

Many studies indicated that the use of MHT may be an important determinant of the concentration of Pb in blood and bones. Irrespective of other factors, it was confirmed that in postmenopausal women who applied MHT the level of Pb was lower, compared to those who had never received such a treatment [26, 27]. These results are consistent with the results of own studies in which a lower level of Pb was also noted in the group of women who used MHT. This confirms that loss of bone mass associated with decreased ovarian function and estrogen deficiency plays an important role in the increase in the level of Pb in blood [28]. The results of clinical studies showed that menopausal estrogen hormone replacement therapy results in a significant reduction of bone mass [29].

Studies carried out by Nash et al. confirmed that an elevated level of Pb in the blood in postmenopausal women results in the development of arterial hypertension, leading to an increased risk of death due to myocardial infarction and cerebral stroke [30].

The increase in the level of Pb in the blood of menopausal women was affected by such factors as: urban place of residence, tobacco smoking, alcohol consumption, time elapsed from the final menstruation. A lower level of this metal-containing toxin was associated with breast feeding, moderate physical activity, presence of Ca in diet, and use of estrogen replacement therapy [31]. Mg supplementation may result in the reduction of Pb and Cd content in the hair in children and adults alike [16].

The results of studies conducted by Akesson et al. indicate that exposure to even low doses of Cd may have a negative effect in the form of bone damage. An increased bone resorption, typical of menopause, favours an increase in the symptoms of osteoporosis in women exposed to this metal-containing toxin [32]. Own studies did not show any significant differences in the level of Cd in women who use MHT, compared to the control group; however, all the women in the study had a considerably elevated level of Cd in their blood.

CONCLUSIONS

1. Higher levels of Mg and Zn in blood plasma were found in women who use MHT.
2. The mean level of Cd in the blood of women in both groups was similar.
3. In women who use MHT the level of Pb in the whole blood was lower than in the rest of the women.

REFERENCES

1. Taylor HS, Manson JE. Update in Hormone Therapy Use in Menopause. J Clin Endocrinol Metab. 2011; 96(2): 255-264.
2. Marara-Studziańska M, Wdowiak A, Bakalczuk G, Bakalczuk S. Wpływ terapii hormonalnej na poziom depresji i jakość życia kobiet w wieku około menopauzalnym, zamieszkujących tereny wiejskie. Przegl Menopauz. 2009; 5: 284-289.
3. Heiss G, Wallace R, Anderson GL, Aragaki A, Beresford SA, Brzyski R, et al. WHI Investigators. Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. JAMA 2008; 299: 1036–1045.
4. Song CH, Barrett-Connor E, Chung JH, Kim SH, Kim KS. Associations of calcium and magnesium in serum and hair with bone mineral density in premenopausal women. Biol Trace Elem Res. 2007; 118(1): 1-9.
5. Hasik J, Hryniewiecki L, Grzymisławski M. Dietetyka. Wydawnictwo Lekarskie PZWL, Warszawa 1999: 48-50.
6. Davis SR. Menopause: New therapies. MJA 2003; 178: 634-637.
7. Fitzpatrick LA, Santen RJ. Editorial: Hot Flashes: The Old and the New, What Is Really true? Mayo Clin Proc. 2002; 77: 1155-1158.
8. Baber R. Phytoestrogens and post reproductive health. Maturitas. 2010; 66: 344-9.
9. Toxicological profile for lead. U.S. Department of Health and Human Services. Public Health Service. Agency for Toxic Substances and Disease Registry, 2007.
10. Szkup-Jabłońska M, Karakiewicz B, Grochans E, Jurczak A, Nowak-Starz G, Rotter I, Prokopowicz A. Effects of blood lead and cadmium levels on the functioning of children with behaviour disorders in the family environment. Ann Agric Environ Med. 2012; 19(2): 241-246.
11. Borja-Aburto VH, Hertz-Picciotto I, Lopez MR, et al. Blood lead levels measured prospectively and risk of spontaneous abortion. Am J Epidemiol. 1999; 150: 590-597.
12. Sallmén M, Lindbohm ML, Anttila A, et al. Time to pregnancy among the wives of men occupationally exposed to lead. Epidemiology 2000; 11: 141-147.
13. Chan OY, Poh SC, Lee HS, et al. Respiratory function in cadmium battery workers: A followup study. Ann Acad Med Singapore. 1988; 17: 283-287.
14. Olewińska E, Kasperczyk A, Kapka L, Kozłowska A, Pawlas N, Dobrakowski M, Birkner E, Kasperczyk S. Level of DNA damage in lead-exposed workers. Ann Agric Environ Med. 2010; 17(2): 231-6.
15. Draft Toxicological profile for cadmium. U.S. Department of Health and Human Services. Public Health Service. Agency for Toxic Substances and Disease Registry, 2008.
16. Sałacka A, Kozielec T, Karakiewicz B. Zawartość kadmu i cynku we włosach u ludzi dorosłych po doustnej suplementacji magnezu. Med Środowiskowa 2010; 13(1): 60-64.
17. Cyril Long. Biochemists handbook. D.Van Nostrand Company. Princeton, New Jersey 1964.
18. Meram I, Balat O, Tamer L, Ugur MG. Trace elements and vitamin levels in menopausal women receiving hormone replacement therapy. Clin Exp Obstet Gynecol. 2003; 30(1): 32-4.
19. Bureau I, Anderson RA, Arnaud J, Raysiguier Y, Favier AE, Roussel AM. Trace mineral status in post menopausal women: impact of hormonal replacement therapy. J Trace Elem Med Biol. 2002; 16(1):9-13.
20. Seelig MS, Altura BM, Altura BT. Benefits and Risks of Sex Hormone Replacement in Postmenopausal Women. J Am Coll Nutr. 2004; 23(5): 482S-496S.
21. Welton AJ, Vickers MR, Kim J, Ford D, Lawton BA, MacLennan AH, Meredith SK, Martin J, Meade TW. WISDOM team. Health related quality of life after combined hormone replacement therapy: randomised controlled trial. BMJ 2008; 337: a1190.
22. Sunar F, Gormus ZI, Baltaci AK, Mogulkoc R. The effect of low dose zinc supplementation to serum estrogen and progesterone levels in post-menopausal women. Biol Trace Elem Res. 2008; 126(1): S11-4.
23. Sunar F, Baltaci AK, Ergene N, Mogulkoc R. Zinc deficiency and supplementation in ovariectomized rats: their effect on serum estrogen and progesterone levels and their relation to calcium and phosphorus. Pak J Pharm Sci. 2009; 22(2): 150-4.
24. Nilsson U, Atewell R, Christoffersson JO, et al. Kinetics of lead in bone after end of occupational exposure. Pharmacol Toxicol. 1991; 69: 477–484.
25. Potula V, Kaye W. The impact of menopause and lifestyle factors on blood and bone lead levels among female former smelter workers: The Bunker Hill Study. Am J Ind Med. 2006; 49: 143–152.
26. Webber CE, Chettle DR, Bowins RJ, et al. Hormone replacement therapy may reduce the return of endogenous lead from bone to the circulation. Environ Health Perspect. 1995; 103: 1150–1153.
27. Hu FB, Grodstein F. Postmenopausal hormone therapy and the risk of cardiovascular disease: The epidemiologic evidence. Am J Cardiol. 2002; 90: 26F–29F.
28. Symanski E, Hertz PI. Blood lead levels in relation to menopause, smoking, and pregnancy history. Am J Epidemiol. 1995; 141: 1047-1058.
29. Genant HK, Cann CE, Ettinger B, Gordan GS. Quantitative computed tomography of vertebral spongiosa: A sensitive method for detecting early bone loss after oophorectomy. Clin Orthop. 2002; 372: 3–8.
30. Nash D, Magder L, Lustberg M, Sherwin RW, Rubin RJ, Kaufmann RB, Silbergeld EK. Blood lead, blood pressure, and hypertension in perimenopausal and postmenopausal women. JAMA. 2003; 289(12): 1523–1532.
31. Muldoon SB, Cauley JA, Kuller LH, et al. Lifestyle and sociodemographic factors as determinants of blood lead levels in elderly women. Am J Epidemiol. 1994; 139: 599-608.
32. Akesson A, Bjellerup P, Lundh T, Lidfeldt J, Nerbrand C, Samsioe G, Skerfving S, Vahter M. Cadmium-induced effects on bone in a population-based study of women. Environ Health Perspect. 2006; 114(6): 830-4.