EFFECTS OF ESTROGEN ON CORONARY ARTERY CALCIFICATION AND THE RELATIONSHIP BETWEEN OSTEOPOROSIS AND CARDIOVASCULAR DISEASES IN POSTMENOPAUSAL WOMEN

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ABSTRACT

Estrogen deficiency is known to be one of the causes of cardiovascular disease and osteoporosis in postmenopausal women. Coronary artery calcification is one of the major factors of cardiovascular disease. The studies related to the effects of estrogen on coronary artery calcification and the possible relation between osteoporosis and cardiovascular disease rapidly increased in recent years. Estrogen levels decrease in postmenopausal women and can lead to an increased risk of cardiovascular disease. Estrogen could affect cardiovascular diseases by mediating the receptor activator of nuclear factor-kappa B ligand-osteoprotegerin system in vascular smooth muscle cells and autophagy in cardiomyocytes. Current evidence indicates that estrogen has an increasing effect on bone mineral density by multiple biochemical pathways: increasing calcium absorption in the gastrointestinal system, decreasing excretion of calcium in the kidneys, reducing bone resorption, such as enchanting osteoblasts, suppressing osteoclasts by inhibiting proinflammatory cytokines, and inhibiting the activity of osteoclasts by essentially inhibiting the receptor activator of nuclear factor-kappa B ligand-osteoprotegerin system. Recent studies showed a significant relationship between coronary artery calcification and osteoporosis due to estrogen's role in these pathogeneses, which can be prevented by using estrogen hormone therapy for post-menopausal women. In this review, we focused on the molecular mechanisms of estrogen in the development of coronary artery calcification and osteoporosis and the effects of estrogen hormone therapy on cardiovascular diseases in postmenopausal women. ***Keywords:*** Menopause, osteoporosis, vascular calcification, estrogen replacement therapy, cardiovascular diseases

INTRODUCTION

Cardiovascular diseases and osteoporosis caused by estrogen deficiency are seen widely in postmenopausal women, causing numerous health risks (1-6). Cardiovascular diseases are correlated with fat deposits and plaques formed in the arteries, which can lead to an increased risk of myocardial infarction (2, 3). Moreover, coronary artery calcification (CAC) is one of the major causes of cardiovascular diseases since it forms calcium plaques in coronary arteries and causes atherosclerosis (4).

Calcium plaque in the arteries contains fat, cholesterol, calcium, and other elements found in the blood (5). In time, plaque solidifies, enlarges, thus decreasing the lumen of the arteries, causing impaired blood flow (5). This situation may end up with ischemia or myocardial infarction (5). According to the World Health Organization's (WHO) data, cardiovascular disease is the most common cause of death in the world, causing over 18 million deaths per year which corresponds to 31 percent of total deaths worldwide (5).

Additionally, estrogen deficiency in postmenopausal women can commonly lead to osteoporosis (6, 7). It has been described by WHO that patients who have a bone mineral density (BMD) below -2.5 standard deviation, calculated by dual-emission X-ray absorptiometry, is classed as having osteoporosis (6). Thus, an increased risk of bone fractures and destruction of the microstructure of bones are observed in osteoporosis (6, 7). However, the relationship between postmenopausal osteoporosis and CAC in postmenopausal women is unclear (6, 8).

Here, we want to draw attention to questions such as whether estrogen hormone therapy is effective on CAC and whether there is a relationship between CAC and osteoporosis in post-menopausal woman. Molecular mechanisms of the effects of estrogen on CAC and osteoporosis should be understood thoroughly to answer these questions. Therefore, we focused on the molecular mechanisms of estrogen on CAC and osteoporosis, and we explained the efficiency of estrogen hormone therapy on CAC in post-menopausal women.

THE EFFECT OF ESTROGEN ON CORONARY ARTERY CALCIFICATION

It is known that CAC is an indicator of coronary plaque burden (9). CAC has been observed more frequently in men than women and its prevalence increases among older-aged men (10). There are many studies about how estrogen affects coronary artery calcification. One of the studies related to osteoprotegerin (OPG) and receptor activator of nuclear factor-kappa B ligand (RANKL) reported that OPG and RANKL are new associates of the tumor necrosis factor signaling superfamily and both are thought to take part in vascular calcification and bone remodeling (11).

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Received: 09.09.2021 Accepted: 23.09.2021 • DOI: 10.4274/tmsj.galenos.2021.08.03.03

Available at https://tmsj.trakya.edu.tr

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Cite this article as:
Güvenç A, Yılmaz C, Balta B et al. Effects of estrogen on coronary artery calcification and the relationship between osteoporosis and cardiovascular diseases in postmenopausal women. Turkish Med Stud J 2021;8(3):99-102.

Although Bakhireva et al. (11) demonstrated that RANKL and OPG's effects on BMD-CAC are minimal, previous studies have shown the importance of RANKL and OPG. As shown in Figure 1, matrix Gla protein (MGP) is a protein that decreases vascular calcification, and bone morphogenetic protein-2 (BMP-2) is a protein that increases vascular calcification. It is shown by Osako et al. (12) that RANKL decreases MGP and increases BMP-2; therefore, RANKL increases vascular calcification non-directly. Osako et al. (12) have also reported that the ratio of RANKL mRNA and BMP-2 in mice that have gone through ovariectomy, and therefore have an estrogen deficiency, have been observed significantly higher compared to controls. Additionally, CAC and atherosclerosis have been observed in mice that have been ovariectomized (12). Hence, estrogen has been demonstrated to have a counter effect on CAC by mediating the RANKL-OPG system (12).

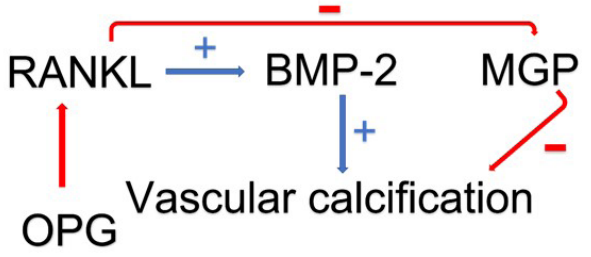

Figure 1: Molecular mechanisms of the RANKL-OPG system. ***OPG:*** Osteoprotegerin, ***RANKL:*** Receptor activator of nuclear factor-kappa B ligand, ***BMP-2:*** Bone morphogenetic protein-2, ***MGP:*** Matrix Gla protein

On the other hand, the main focus of current research is on the effect of heart fat on CAC. Heart fat is one of the causes of coronary artery disease, and the contents of heart fat increase after menopause (13). According to this research, using transdermal β17-estradiol positively affects the connection between pericardial adipose tissue accumulation and CAC progression (13). In addition, it has been observed that using oral conjugated equine estrogens might decelerate epicardial adipose tissue accumulation (13).

Another molecular research area on the possible effects of estrogen on calcification includes autophagy. Autophagy is defined as the self-destruction of a cell to obtain new and healthier cells. Autophagy functionally supports the inhibitory effects of estrogen on vascular calcification as demonstrated by Peng et al. (14). In addition, recent findings show that some molecular and functional alterations in the homeostasis-related proteins in cardiomyocytes are caused by a lack of estrogen (15). Deterioration of the calcium homeostasis cycle has been reported to have negative effects on cardiac function, therefore deterioration of the calcium homeostasis cycle causes pathological mechanisms of a variety of cardiovascular diseases (15).

ESTROGEN HORMONE THERAPY AND CORONARY ARTERY CALCIFICATION

Estrogen increases nitric oxide production, which vasodilates arteries and enhances vascular function, and lessens the development of atheroma by reducing endothelin-1 release and angiotensin-1-converting-enzyme activity, modulating ion channels, and reducing the modification of vascular remodeling processes (16). CAC is known as an important determinant of cardiovascular risk and it is known to be associated with atherosclerosis and future cardiac problems (17). Schierbeck et al. (18) found in their analyses of 1006 women in Denmark that hormone replacement therapy (HRT) users have decreased risk of mortality, heart failure, or myocardial infarction and no increase in venous thromboembolism, stroke, or cancer. Many studies have been conducted to study the association between estrogen and CAC in postmenopausal women (17, 19, 20). A previous study of 1064 patients aged 50-59 years showed that 537 of them received 0.625 mg/day estrogen and 527 of them received a placebo for 7.4 years (19). The results of this study have shown that women who took long-term estrogen therapy had a noticeably lower coronary artery calcification ratio (19). Similar to these findings, a study on 2213 postmenopausal women of Akhrass et al. (20) indicated that HRT users are very likely to have less coronary artery calcium scores and it has been observed that they unlikely have high coronary artery calcium scores. In another study on the younger aged midlife women compared to postmenopausal women showed a significant relationship between HRT usage and a decrease in coronary artery calcification (21). According to the findings above, estrogen HRT can be accepted as protective on coronary artery calcification among different age groups.

In a clinical study run by the Women's Health Initiative (WHI), no reduction was found in coronary heart disease between patients on HRT, but more effective distribution of low-density lipoprotein subclasses have been shown in blood lipid concentrations (22). To understand this finding better, the Healthy Women Study was carried out to study the prevalence of CAC and lipoprotein levels of women on HRT (22). Compared with nonusers, HRT users had higher levels of very-low-density lipoprotein particles (triglycerides) and did not have a better low-density lipoprotein subclass distribution, which may explain the failure of hormone therapy to be associated with a difference in CAC in our study or with a reduction in coronary heart disease risk in randomized clinical trials (22). The WHI study was a randomized clinical trial conducted among postmenopausal women aged 50-79 years (23). One group was given a placebo and the other group was given conjugated equine estrogen, and no significant association between estrogen therapy use and reduced risk of coronary heart disease was found (23). However, as an ancillary study, the WHI Coronary Artery Calcification Study found an association between estrogen use and reduced risk of coronary heart disease (23).

The effects of estrogen as a single hormone therapy agent or combination of other hormone agents have been investigated. In a study run by the WHI, it was found that the use of estrogen and progestin (combined) hormone therapy caused a minor but significant uprise in cardiovascular event risk, and in breast cancer risk in asymptomatic participants (24). Budoff et al. (24) carried out a study to investigate whether estrogen-alone hormone therapy affected cardiovascular risk. To do so, they separated participants into three groups; no hormone, estrogen, and progestin (combined), and estrogen-only hormone replacement therapy users (24). In this observational study, they also found that there was no benefit of combined therapy to reduce coronary heart risk compared to non-users (24). Interestingly, the level of atherosclerosis was found to be lower in participants using estrogen-only hormone replacement therapy than in those using combined therapy and not using replacement therapy (24).

In a previous study, the relationship between BMD and CAC in females who use or do not use estrogen hormone therapy has been compared with males (25). An inverse association of BMD and CAC was found only in participants who were using estrogen hormone therapy, whereas no statistically significant association was observed in both the female participants who were not taking hormone therapy and in male participants (25). According to the study, estrogen was found to increase BMD and reduce CAC (25).

The degree of the relationship between estrogen hormone therapy and BMD and CAC is not exactly known (25).

A study that investigates the link between HRT, CAC, and carotid intima-media thickness in postmenopausal women showed a low but not significant prevalence of CAC among estrogen hormone therapy users (26).

THE EFFECTS OF ESTROGEN ON OSTEOPOROSIS

Estrogen is effective in multiple mechanisms underlying the regulation of calcium homeostasis and bone remodeling to prevent osteoporosis. These critical biological mechanisms occur by enhancing calcium absorption in the gastrointestinal system and reducing the excretion of calcium from the kidneys (27, 28). Moreover, estrogen may negatively regulate the activity of osteoclasts (large bone tissue cells that are responsible for bone resorption) by the inhibition of some proinflammatory cytokines such as interleukin-1, interleukin-6, tumor necrosis factor-α, macrophage colony-stimulating factor, and PGE26. Thus, it is reported that bone resorption decreases with estrogen (29).

Additionally, according to current findings, the effects of estrogen on BMD may result from the regulator role of estrogen on OPG and its ligand RANKL which are shown as the new-found associates of the tumor necrosis factor-signaling family as mentioned above (30). Estrogen reduces bone resorption by inhibiting pro-resorptive cytokines and suppressing RANKL (30). In addition, it has been shown that estrogen boosts osteoclast apoptosis (31). Furthermore, estrogen positively regulates cell differentiation into the osteoblasts and mediates adipocyte lineage cells to shift into the osteoblast (32).

Likewise, one of the effects of estrogen on vascular tissues is the inhibition of vascular smooth muscle cells (VSMC) (29, 33). These cells are the progenitors of the osteoblast-like cells, and they generate matrix proteins such as osteocalcin, osteonectin, osteopontin that are responsible for vascular calcification (29, 33). Interestingly, suppression of tumor necrosis factor-α in bone tissues reduces the bone resorption, preventing osteoporosis; whereas in vascular tissues, the proliferation of VSMC decreases vascular calcification and reduces coronary heart disease risk by reducing the calcium burden (29, 33). In recent studies, scientists have found this reducing effect on vascular calcification with suppression of the VSMC proliferation only occurs in female animals (29, 33). According to previous findings, a relationship between vascular calcification and osteoporosis could be possible.

OSTEOPOROSIS AND VASCULAR CALCIFICATION

Recent studies suggest that mechanisms of osteoporosis may be related to vascular calcification in postmenopausal women (12, 34). Since CAC shares a similar cardiovascular disease risk with other vascular calcification types, such as general aortic calcification, the relationship between CAC and osteoporosis needs to be clarified.

As shown in Figure 2, menopause induces estrogen deficiency, causing an increase in RANKL levels in the vascular calcification signaling pathway. In this pathway, RANKL may trigger BMP-2 levels to increase and MGP levels to decrease during vascular calcification (12). Similarly, estrogen deficiency causes osteoporosis in postmenopausal by upregulating the RANKL signaling pathway (30, 35, 36).

Many studies in the latest literature reported an inverse relationship between BMD and aortic calcification (increased calcium burden in arteries) (37, 38). A study by Tankó et al. (38) reported that osteoporosis, which causes a high bone fracture risk in hips, may be a predictor of an increased risk factor for coronary heart diseases caused by aortic calcification. Furthermore, Schulz et al. (39) demonstrated that heart disease has been linked to osteoporosis and aortic calcification and that osteoporosis can be accepted as a significant predictor of a decrease in BMD.

Manson et al. (40) reported a statistically significant decrease in coronary heart disease risk in postmenopausal women who took equine estrogen compared to postmenopausal women who took a placebo. These results point to the mediator role of estrogen in CAC. Bakhireva et al. (25) reported a significant association between CAC and osteoporosis in postmenopausal women who use estrogen HRT. The study did not demonstrate a statistically significant association in men and postmenopausal women who has symptomless cardiovascular diseases and who do not use HRT (25). Furthermore, reports of Choi et al. (41) showed a statistically significant association between high-ranking coronary plaque burdens and low-ranking BMD in postmenopausal women, which was independent of the presence of cardiovascular disease and the age of the participants. Similarly, a previous study indicated that estrogen hormone therapy increased BMD and decreased hip and medical vertebral fractures, which gave notable information about the role of estrogen on osteoporosis (42).

Even though there are contradictory findings that have not found a statistically significant relationship between CAC and osteoporosis, further studies that include patients who have coronary heart disease or osteoporosis are needed (43, 44). These studies would be important in understanding the link between CAC and osteoporosis.

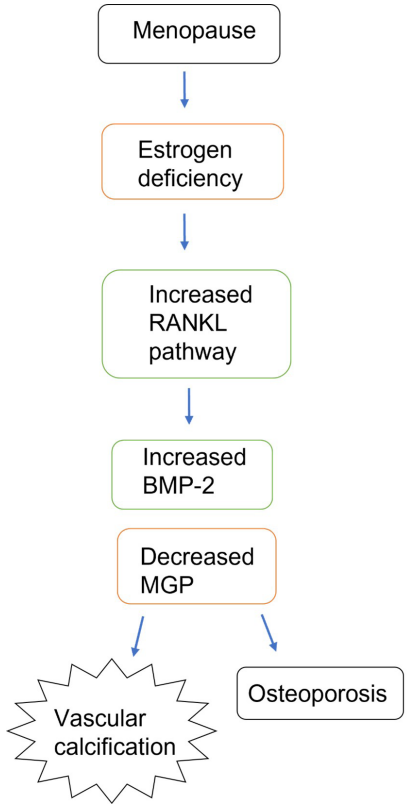

Figure 2: The relationship between vascular calcification and osteoporosis.
RANKL: Receptor activator of nuclear factor-kappa B ligand, ***BMP-2:*** Bone morphogenetic protein-2, ***MGP:*** Matrix Gla protein

CONCLUSION

In conclusion, decreasing estrogen levels in postmenopausal women may be responsible for creating an increased risk of cardiovascular disease. Estrogen could increase the risk of cardiovascular disease by upregulating the RANKL-OPG system in vascular smooth muscle cells and autophagy in cardiomyocytes. Additionally, regulation of calcium homeostasis is important since estrogen deficiency causes molecular and functional changes in calcium homeostasis-related proteins in cardiomyocytes. Estrogen therapy has been demonstrated to be effective on osteoporosis by similar biochemical pathways. Clarifying the association between osteoporosis and cardiovascular diseases in postmenopausal women is essential to better understand the efficiency of estrogen hormone therapy. Further studies are needed to achieve this.

Ethics Committee Approval: N/A
Informed Consent: N/A
Conflict of Interest: The authors declared no conflict of interest.
Author Contributions: Concept: AG, CY, BB, ZY, SAV. Design: AG, CY, BB, ZY, SAV. Supervision: AG, CY, BB, ZY, SAV. Resources: AG, CY, BB, ZY, SAV. Materials: AG, CY, BB, ZY, SAV. Data collection and/or processing: AG, CY, BB, ZY, SAV. Analysis and/or Interpretation: AG, CY, BB, ZY, SAV. Literature Search: AG, CY, BB, ZY, SAV. Writing Manuscript: AG, CY, BB, ZY, SAV. Critical Review: AG, CY, BB, ZY, SAV.
Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Liu W, Zhang Y, Yu CM et al. Current understanding of coronary artery calcification. J Geriatr Cardiol 2015;12(6):668-75.
2. Criqui MH, Denenberg JO, Ix JH et al. Calcium density of coronary artery plaque and risk of incident cardiovascular events. J Am Med Assoc 2014;311(3):271-8.
3. Herrema H, Nieuwdorp M, Groen AK. Microbiome and cardiovascular disease. In: Handbook of Experimental Pharmacology. Berlin, Heidelberg: Springer; 2020.p.1-24.
4. Okamura A, Rakugi H, Ohishi M et al. Upregulation of renin-angiotensin system during differentiation of monocytes to macrophages. J Hypertens 1999;17(4):537-45.
5. Thomas H, Diamond J, Vieco A et al. Global atlas of cardiovascular disease 2000-2016: the path to prevention and control. Glob Heart 2018;13(3):143-63.
6. Armas LAG, Recker RR. Pathophysiology of osteoporosis: new mechanistic insights. Endocrinol Metab Clin North Am 2012;41(3):475-86.
7. Lane JM, Russell L, Khan SN. Osteoporosis. Clin Orthop Relat Res 2000;(372):139-50.
8. Christian RC, Harrington S, Edwards WD et al. Estrogen status correlates with the calcium content of coronary atherosclerotic plaques in women. J Clin Endocrinol Metab 2002;87(3):1062-7.
9. Jin HY, Weir-McCall JR, Leipsic JA et al. The relationship between coronary calcification and the natural history of coronary artery disease. JACC Cardiovasc Imaging 2021;14(1):233-42.
10. Mohan J, Bhatti K, Tawney A et al. Coronary artery calcification. [Updated 2021 Aug 13]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan. Available from: URL: https://www.ncbi.nlm.nih.gov/books/NBK519037/.
11. Bakhireva LN, Laughlin GA, Bettencourt R et al. Does osteoprotegerin or receptor activator of nuclear factor-kappa B ligand mediate the association between bone and coronary artery calcification. J Clin Endocrinol Metab 2008;93(5):2009-12.
12. Osako MK, Nakagami H, Koibuchi N et al. Estrogen inhibits vascular calcification via vascular RANKL system: common mechanism of osteoporosis and vascular calcification. Circ Res 2010;107(4):466-75.
13. El Khoudary SR, Zhao Q, Venugopal V et al. Effects of hormone therapy on heart fat and coronary artery calcification progression: secondary analysis from the KEEPS trial. J Am Heart Assoc 2019;8(15):e012763.
14. Peng YQ, Xiong D, Lin X et al. Oestrogen inhibits arterial calcification by promoting autophagy. Sci Rep 2017;7(1):3549.
15. Jiao L, Machuki JO, Wu Q et al. Estrogen and calcium handling proteins: new discoveries and mechanisms in cardiovascular diseases. Am J Physiol Heart Circ Physiol 2020;318(4):H820-9.
16. Stevenson JC. Does estrogen therapy reduce coronary artery calcification in postmenopausal women? Nat Clin Pract Cardiovasc Med 2007;4(12):654-5.
17. Mendelsohn ME, Karas RH. HRT and the young at heart. N Engl J Med 2007;356(25):2639-41.
18. Schierbeck LL, Rejnmark L, Tofteng CL et al. Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial. BMJ 2012;345:e6409.
19. Manson JE, Allison MA, Rossouw JE et al. Estrogen therapy and coronary-artery calcification. N Engl J Med 2007;356(25):2591-602.
20. Akhrass F, Evans AT, Wang Y et al. Hormone replacement therapy is associated with less coronary atherosclerosis in postmenopausal women. J Clin Endocrinol Metab 2003;88(12):5611-4.
21. Weinberg N, Young A, Hunter CJ et al. Physical activity, hormone replacement therapy, and the presence of coronary calcium in midlife women. Women Heal 2012;52(5):423-36.
22. Mackey RH, Kuller LH, Sutton-tyrrell K. Hormone therapy, lipoprotein subclasses, and coronary calcification. Arc Intern Med 2005;165(5):510-5.
23. Poornima IG, Mackey RH, Allison MA et al. Coronary artery calcification (CAC) and post-trial cardiovascular events and mortality within the Women's Health Initiative (WHI) estrogen-alone trial. J Am Heart Assoc 2017;6(11):e006887.
24. Budoff MJ, Chen GP, Hunter CJ et al. Effects of hormone replacement on progression of electron beam tomography. J Women's Health 2005;14(5):410-7.
25. Bakhireva LN, Barrett-Connor EL, Laughlin GA et al. Differences in association of bone mineral density with coronary artery calcification in men and women: the Rancho Bernardo Study. Menopause 2005;12(6):691-8.
26. Shahar E, Burke GL, Cushman M et al. Post menopausal hormones and measures of subclinical atherosclerosis: the multi-ethnic study of atherosclerosis. Preventive Medicine 2008;47:38-45.
27. Irnaten M, Blanchard-Gutton N, Harvey BJ. Rapid effects of 17β-estradiol on epithelial TRPV6 Ca2+ channel in human T84 colonic cells. Cell Calcium 2008;44(5):441-52.
28. Öz OK, Hajibeigi A, Howard K et al. Aromatase deficiency causes altered expression of molecules critical for calcium reabsorption in the kidneys of female mice. J Bone Miner Res 2007;22(12):1893-902.
29. Christian RC, Harrington S, Edwards WD et al. Estrogen status correlates with the calcium content of coronary atherosclerotic plaques in women. J Clin Endocrinol Metab 2002;87(3):1062-7.
30. Riggs BL. The mechanisms of estrogen regulation of bone resorption. J Clin Invest 2000;106(10):1203-4.
31. Chen X, Wang Z, Duan N et al. Osteoblast-osteoclast interactions. Connect Tissue Res 2018;59(2):99-107.
32. Siddiqui JA, Swarnkar G, Sharan K et al. 8,8"-Biapigeninyl stimulates osteoblast functions and inhibits osteoclast and adipocyte functions: osteoprotective action of 8,8"-biapigeninyl in ovariectomized mice. Mol Cell Endocrinol 2010;323(2):256-67.
33. Fitzpatrick LA. Gender-related differences in the development of atherosclerosis: studies at the cellular level. Clin Exp Pharmacol Physiol 1996;23(3):267-9.
34. Hofbauer LC, Brueck CC, Shanahan CM et al. Vascular calcification and osteoporosis--from clinical observation towards molecular understanding. Osteoporos Int 2007;18(3):251-9.
35. Wu M, Rementer C, Giachelli CM. Challenges in treatment. Calcif Tissue Int 2013;93(4):365-73.
36. An WS. Sex hormones impact vascular calcification and fracture in dialysis patients. Kidney Res Clin Pract 2020;39(3):236-8.
37. Frye MA, Melton LJ, Bryant SC et al. Osteoporosis and calcification of the aorta. Bone Miner 1992;19(2):185-94.
38. Tankó LB, Bagger YZ, Christiansen C. Low bone mineral density in the hip as a marker of advanced atherosclerosis in elderly women. Calcif Tissue Int 2003;73(1):15-20.
39. Schulz E, Arfai K, Liu X et al. Aortic calcification and the risk of osteoporosis and fractures. J Clin Endocrinol Metab 2004;89(9):4246-53.
40. Manson JE, Allison MA, Rossouw JE et al. Estrogen therapy and coronary-artery calcification. N Engl J Med 2007;356(25):2591-602.
41. Choi SH, An JH, Lim S et al. Lower bone mineral density is associated with higher coronary calcification and coronary plaque burdens by multidetector row coronary computed tomography in pre- and postmenopausal women. Clin Endocrinol 2009;71(5):644-51.
42. Cauley JA. Estrogen and bone health in men and women. Steroids 2015;99(Part A):11-5.
43. Barengolts EI, Herman M, Kukreja SC et al. Osteoporosis and coronary atherosclerosis in asymptomatic postmenopausal women. Calcif Tissue Int 1998;62(3):209-13.
44. Sinnott B, Syed I, Sevrukov A et al. Coronary calcification and osteoporosis in men and postmenopausal women are independent processes associated with aging. Calcif Tissue Int 2006;78(4):195-202.