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Review Article

The Role of Vitamin D in Menopausal Medicine

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Menopause is the time at which menstruation stops in women. After menopause, women are more susceptible to some diseases, especially osteoporosis and cardiovascular disease. Vitamin D has a protective effect against osteoporosis by facilitating the absorption of calcium and affecting parathyroid hormone. Vitamin D also affects cardiovascular function by lowering the blood pressure, which affects the renin-angiotensin system and alters the low-density lipoprotein receptor activity. This paper discusses supplemental vitamin D in postmenopausal women with osteoporosis and cardiovascular disease.

Key Words: Cardiovascular disease, menopause, osteoporosis, vitamin D

Menopause occurs when women stop producing female hormones and ovulating. Typically, it occurs in women older than 50 years. Women undergo many physiological changes during menopause, and some diseases are more prevalent in postmenopausal women, including osteoporosis, cardiovascular disease, cancers of the vagina and uterus, and altered cognitive function. Osteoporosis is associated with reductions in the integrity and strength of bone, which are accompanied by an increased fracture risk. The main causes of cardiovascular disease are arteriosclerosis, hypertension, degenerative changes, and heredity. Vitamin D can have a significant impact on postmenopausal women, potentially improving postmenopausal problems via several mechanisms. First, vitamin D promotes calcium absorption in the digestive tract, which affects bone density and bone metabolism.[1] It is also an intrinsic suppressor of the renin-angiotensin system (RAS) and is essential to maintain normal cardiovascular homeostasis because of lower blood pressures.[2] Calcium and phosphorus in skeletal muscle regulate the absorption of calcium and phosphorus mineralization in the metabolism of bone.[3] Vitamin D is believed to benefit postmenopausal women.[4,5] We

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investigated the role of vitamin D in postmenopausal women.

MENOPAUSAL SYMPTOMS

Menopause is a time of great change when viewed in a social context, and postmenopausal women undergo physical and mental changes. Common symptoms are memory loss, facial blushing, and exhaustion in women at the menopause transition. Korean middle-aged women develop low-level depression, a slightly elevated degree of self-identity, and relatively fewer climacteric symptoms.[6,7] A decrease in serotonin during menopause results in hot flashes.[8] Despite recognizing the symptoms of menopause, many women do not seek treatment. Knowledge of menopause differs with age, and young women with more education tend to know more about menopause. Vitamin D has the potential to affect menopause symptoms because a lack of vitamin D results in failure of calcium binding in bone. In addition, vitamin D controls the calcium concentration in cells and improves muscle function. The risk of falling increases when there is insufficient vitamin D.

OSTEOPOROSIS

The incidence of osteoporosis increases after menopause, and the prevalence of osteoporosis is increasing with the recent increase in the elderly population.[9] In patients with osteoporosis, the strength of bone is reduced and the risk of fracture increases. Enhanced estrogen during menopause can reduce the risk of postmenopausal osteoporosis. The primary role of vitamin D is maintenance of normal muscle mass and function, which reduces the risk of falling. The active form of vitamin D, 1,25-dihydroxyvitamin D_3 [1,25 $(OH)_2D_3$], stimulates the formation of intestinal intracellular calcium-binding proteins, opens calcium channels, and stimulates intestinal calcium and phosphorus absorption.[1] When vitamin D is lacking, the $1,25(OH)_2D_3$ levels fall and less calcium is available for bone mineralization.[1] A low serum calcium concentration stimulates increased PTH secretion,10 which stimulates bone turnover and leads to bone loss.[1,10] Vitamin D deficiency also leads to secondary hyperparathyroidism, a calcium-induced increase in the secretion of parathyroid hormone, and high bone turnover, which leads to bone disease.[1]

There is a relationship between bone mineral density (BMD) and serum 25-hydroxyvitamin D_3 [$25(OH)D_3$].[11,12] BMD is an index used to diagnose the risk of osteoporosis and fracture. A low BMD reflects a low bone density and an increased risk of osteoporosis.[13] A study of postmenopausal women with osteoporosis in Amsterdam found a significant positive correlation between the vitamin D status and BMD,[11,12] and the critical serum $25(OH)D_3$ level was 50 nmol/L.[14] Vitamin D supplements reduce the risk of fractures by reducing PTH secretion and increasing bone density. In one study of healthy postmenopausal women, vitamin D and calcium did not significantly reduce hip fractures, although bone density had improved.[15]

Hormone therapy for menopausal women can also affect bone density, and vitamin D should have a synergistic effect.[16]

JOINTS

A gradual increase in joint symptoms is common in menopausal women via the influence of vitamin D, and joint symptoms can progress more quickly in vitamin D deficiency. One placebo-controlled clinical trial of the impact of vitamin D on joint symptoms in postmenopausal women found no difference in the incidence or severity of joint symptoms between vitamin D supplementation and placebo.[17] Therefore, women taking calcium plus vitamin D should not expect an easing of joint symptoms.

CANCERS

The cause of pancreatic cancer is unclear. The risk of pancreatic cancer increases with an age of > 45 years; smoking history; history of head and neck, lung, or bladder cancer; diabetes; and high fat and food intake. Pancreatic cancer rates are increased in patients with chronic pancreatitis. One prospective cohort study examined whether vitamin D alters the risk and mortality of pancreatic cancer, but did not find a large difference between the study group and the group with insufficient vitamin D.[18] Vitamin D deficiency has an adverse affect on colorectal cancer, while high vitamin D significantly lowers the risk of death from colorectal cancer. More research should be performed to examine the role of vitamin D in malignancy.

CARDIOVASCULAR SYSTEM

Lack of vitamin D inhibits the RAS, which negatively influences cardiovascular disease.[2] In the RAS, the kidney secretes renin when the blood pressure drops, and renin is converted into angiotensin II by angiotensin-converting enzyme and then into angiotensin I in the liver, which increases the blood pressure. A knock-out study provided evidence that $1,25(OH)_2D_3$ is involved in regulating the RAS by inhibiting renin gene expression and reducing the activity of the cAMP response element.[19,20] Numerous studies have found that serum $1,25(OH)_2D_3$ levels are inversely proportional to the blood pressure in normotensive individuals and hypertensive patients. $1,25(OH)_2D_3$ negatively controls the endocrine regulation of the RAS and cardiovascular function by interrupting the signal transmission path, reducing the synthesis of renin.[20] If renin is suppressed, angiotensinogen is not activated by angiotensin I, which adversely affects blood pressure regulation.[21] Vitamin D deficiency also has a negative effect on total cholesterol, LDL cholesterol (LDL-C), and insulin secretion in various ethnic groups.[22] LDL-C is responsible for transporting liver-produced cholesterol to the tissues. When LDL-C levels increase, cholesterol builds up on the blood vessel walls, causing atherosclerosis. High-density lipoprotein cholesterol (HDL-C) prevents the accumulation of cholesterol. Therefore, vitamin D deficiency has a negative effect on LDL-C, increasing cardiovascular risk. Finally, vitamin D supplementation activates the RAS, re-

ducing LDL-C and positively affecting cardiovascular disease.

UTERUS AND VAGINA

Menopause-associated hormonal changes have many effects on the uterus and vagina.[23,24] Vitamin D affects fertility and alleviates symptoms of vaginal atrophy, along with osteoporosis therapeutics. Vitamin D receptors (VDR) were expressed at a high level on uterus in postmenopause.

HEALTH OUTCOME AND MORTALITY

There has been recent interest in the effect of vitamin D on health. Supplemental calcium and vitamin D can have positive effects on hip fracture and colorectal cancer, but such supplementation does not reduce the risk of invasive breast cancer.[25] A meta-analysis found that vitamin D alone does not affect mortality, but the risk of death was decreased if vitamin D was given with calcium.[26]

In patients with osteoporosis, vitamin D supplementation increases the serum $1,25(OH)_2D_3$ concentration, reducing PTH secretion and inhibiting osteolysis while increasing BMD. In patients with cardiovascular disease, vitamin D influences the RAS and has a positive effect on blood pressure. It also reduces LDL-C accumulation in the blood vessels. Consequently, vitamin D supplementation should lower the risks of postmenopausal osteoporosis, cardiovascular disease, and other diseases.

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COMPETING INTERESTS

The authors declare no conflict of interest.

REFERENCES

1. Lips P, van Schoor NM. The effect of vitamin D on bone and osteoporosis. Best pract Res Clin Endocrinol Metab 2011;25:585-91.
2. Dong J, Lau CW, Wong S, Huang Y. Cardiovascular benefits of vitamin D. Sheng Li Xue Bao 2014;66:30-6.
3. Kim JS, Choi YJ, Lee KW, Song IJ, Kim CA, Son BH, et al. The study in vitamin D concentration in the blood for infants with high level of alkaline phosphatase. Kosin Med J 2012;27:17-24.
4. Kim TH, Lee HH, Kim JM. Letters to the Editor. Menopause 2015;22:797.
5. Kim TH, Lee HH, Kim JM. Comments on vitamin D. Maturitas 2015;81:329.
6. Han MJ, Lee JH. Factors influencing self-identity

and menopausal symptoms on level of depression in middle aged women. Korean J Women Health Nurs 2013;19:275-84.

7. Kwak EK, Park HS, Kang NM. Menopause knowledge, attitude, symptom and management among midlife employed women. J Menopausal Med 2014;20:118-25.
8. LeBlanc ES, Hedlin H, Qin F, Desai M, Wactawski-Wende J, Perrin N, et al. Calcium and vitamin D supplementation do not influence menopause-related symptoms: Results of the Women's Health Initiative Trial. Maturitas 2015;81:377-83.
9. Kim HY, Kong EH. The Association between serum GGT level and bone mineral density in postmenopausal women. Kosin Med J 2013;28:35-41.
10. Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. Endocr Rev 2001;22:477-501.
11. Limpaphayom KK, Kim HY. Diagnosis and treatment of osteoporosis. Kosin Med J 2011;26:121-6.
12. Choi SH, Lee DJ, Kim KM, Kim BT. Association between seasonal changes in vitamin D and bone mineral density. J Korean Soc Menopause 2011;17:88-93.
13. Cândido FG, Bressan J. Vitamin D: link between osteoporosis, obesity, and diabetes? Int J Mol Sci 2014;15:6569-91.
14. Kuchuk NO, Pluijm SM, van Schoor NM, Looman CW, Smit JH, Lips P. Relationships of serum 25-hydroxyvitamin D to bone mineral density and serum parathyroid hormone and markers of bone turnover in older persons. J Clin Endocrinol Metab 2009;94:1244-50.
15. Jackson RD, LaCroix AZ, Gass M, Wallace RB, Robbins J, Lewis CE, et al. Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med 2006;354:669-83.
16. Robbins JA, Aragaki A, Crandall CJ, Manson JE, Carbone L, Jackson R, et al. Women's Health Initiative clinical trials: interaction of calcium and vitamin D with hormone therapy. Menopause 2014;21:116-23.
17. Chlebowski RT, Pettinger M, Johnson KC, Wallace R, Womack C, Mossavar-Rahmani Y, et al. Calcium plus vitamin D supplementation and joint symptoms in postmenopausal women in the women's health initiative randomized trial. J Acad Nutr Diet 2013;113:1302-10.
18. Wolpin BM, Ng K, Bao Y, Kraft P, Stampfer MJ, Michaud DS, et al. Plasma 25-hydroxyvitamin D and risk of pancreatic cancer. Cancer Epidemiol Biomarkers Prev 2012;21:82-91.
19. Norman PE, Powell JT. Vitamin D and cardiovascular disease. Circ Res 2014;114:379-93.
20. Li YC, Qiao G, Uskokovic M, Xiang W, Zheng W, Kong J. Vitamin D: a negative endocrine regulator of the renin-angiotensin system and blood pressure. J Steroid Biochem Mol Biol 2004;89-90:387-92.
21. Li YC. Vitamin D regulation of the renin-angiotensin system. J Cell Biochem 2003;88:327-31.
22. Pérez-López FR. Vitamin D metabolism and cardiovascular risk factors in postmenopausal women. Maturitas 2009;62:248-62.

23. Kim TH, Park J, Lee HH, Lee WS, Chung SH, Park Y, et al Expression of vitamin D receptor by pulse consumption in the uterus of menopausal mouse model. J Korean Soc Menopause 2013;19:1-8.
24. Kim TH, Lee HH, Park J. Immunohistochemical detection of the 1,25-dihydroxy vitamin D receptor in the human vagina. Iran J Reprod Med 2014;12:805-10.
25. Cauley JA, Chlebowski RT, Wactawski-Wende J, Robbins JA, Rodabough RJ, Chen Z, et al. Calcium plus vitamin D supplementation and health outcomes five years after active intervention ended: the Women's Health Initiative. J Womens Health (Larchmt) 2013;22:915-29.
26. Rejnmark L, Avenell A, Masud T, Anderson F, Meyer HE, Sanders KM, et al. Vitamin D with calcium reduces mortality: patient level pooled analysis of 70,528 patients from eight major vitamin D trials. J Clin Endocrinol Metab 2012;97:2670-81.

Peer Reviewer's Commentary

Vitamin D supplementation increases the serum 1,25(OH)2D3 concentration, reducing PTH secretion and inhibiting osteolysis while increasing BMD. In patients with cardiovascular disease, vitamin D influences the RAS and has a positive effect on blood pressure.
In this review, the authors presented a number of function of the Vitamin D. Recently Several Research suggests that women with low levels of vitamin D have a higher risk of breast cancer. Vitamin D may play a role in controlling normal breast cell growth and may be able to stop breast cancer cells from growing. So It should be considered about the tretment level of Vitamin D.

(Editorial Board)