

Review Article

Role of Vitamin D in Health of Post-Menopausal Women

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A B S T R A C T

Menopause is an important stage of a woman's lifetime. The alterations in hormones during menopause transition bring many unfavourable changes in the health of women. A decline in oestrogen levels promotes vitamin D insufficiency which is a serious problem among post-menopausal women. Human beings, especially post-menopausal women, essentially need vitamin D to address the skeletal as well as extra-skeletal demands.

The current review examines the connection between a lack of vitamin D and the occurrence of skeletal disorders, pelvic floor disorders, metabolic syndrome, sleep disorders, depression, anxiety and fall in certain cognitive functions among post-menopausal women. These problems, in addition to various other menopausal symptoms, significantly affect the overall quality of life of women undergoing menopause and dramatically increase the massive load on the healthcare system and cost of living. Limited choice of vitamin D-rich foods, changing hormones and poor sun exposure due to hot climate, lifestyle and cultural factors make women more susceptible to vitamin D deficiency. Hence, there is a need to create awareness about this multi-tasking vitamin and formulate food fortification guidelines and public health policies in accordance with revised recommended dietary intakes.

Keywords: Vitamin D, Menopause, Women, Health

Introduction

All women go through menopause at some point in their life. It is the irreversible termination of menstruation brought on by the ovaries' loss of follicular activity, which in the majority of women, starts declining in the latter years of 30s and reaches its peak in the beginning of 50s.¹ These changes in the women's physiology not only symbolise the cessation of reproductive function but also usher them into a novel stage of life.² While Western women reach menopause nearly at the age of 51 years, their Indian counterparts reach menopause at the age of 46.2 years.³ Due to an increase

in longevity and a correspondingly considerable rise in the world's ageing population, this phenomenon has become a matter of growing concern.

By 2030, there will be 1.2 billion post-menopausal women in the world. The terms menopausal transition and perimenopause can be used interchangeably.¹ Irrespective of whether menopause is natural or induced, the term "post-menopause" is defined as commencing after the final menstrual period (FMP). The entire reproductive phase up to FMP is described as "premenopause".

Menopause is associated with a range of physically

discomforting symptoms, encompassing vaginal mucosal atrophy resulting in dyspareunia, pruritus, and vaginitis; atrophic changes in the genitourinary tract leading to inflammation of urethra, urinary incontinence and increased frequency of urine; vasomotor symptoms such as night sweats and hot flashes; and recurrent urinary tract infections. In addition to gynaecological health concerns stemming from reduced oestrogen levels, menopausal women must contend with weight gain, fatigue, and psychological issues, including grief, irritability, health-related anxiety, and heightened sensitivity. However, it has been challenging to discriminate between symptoms brought on by ovarian function loss and those brought on by ageing or the stresses of midlife.⁴ The symptoms of menopause generally last for four to five years after the FMP, however, some women experience these even up to 12 years after the last menstrual period.⁵

Along with the reproductive system, the central nervous, cardiovascular, immunological, and skeletal systems also depend on oestrogens to function normally.⁶ Oestrogen amplifies the activity of 1- α -hydroxylase, an enzyme produced by the kidneys that governs the activation of vitamin D and facilitates the functioning of the Vitamin D Receptor (VDR). The gradual reduction in ovarian oestrogen production that occurs during menopause is thought to contribute to vitamin D deficiency, primarily due to the decline in VDR levels.⁷

Symptoms such as mood disturbance and musculoskeletal complaints generally accompanying vitamin D deficiency are comparable to the symptoms that some women may face during menopause.⁸ Vitamin D deficiency may be asymptomatic or manifest as weight gain, fractures, fatigue, muscle and joint pains, reduced immunity, gum problems, mood swings, sleeplessness, depression, and dementia.⁹ Numerous research investigations have elucidated vitamin D's multifaceted capacity in mitigating various health conditions, including but not limited to heart disease, cancer, Alzheimer's disease, osteoporosis, depression, immune system function, gain in weight and diabetes. Vitamin D emerges as a versatile micronutrient with the potential to provide protection against a diverse spectrum of diseases. The majority of women in their middle age, however, are vitamin D deficient and do not profit from it.⁹

Deficiency of Vitamin D among Post-Menopausal Women

Post-menopausal women (PMW) are particularly vulnerable to vitamin D deficiency due to factors such as alterations in body composition, advancing age, racial disparities, limited solar contact, inadequate vitamin D intake, and obesity. The relationship between insufficient vitamin D levels and various menopausal health issues, including sexual dysfunction, vasomotor symptoms, urogenital atrophy

and post-menopausal osteoporosis, is becoming more and more obvious from the evidence.¹⁰ Additionally, several epidemiological studies have established a connection between vitamin D insufficiency and an elevated risk of chronic conditions like cancer, diabetes and cardiac diseases, underscoring that vitamin D deficiency has implications beyond musculoskeletal health.¹¹

Prevalence

Numerous investigations conducted across diverse regions of India have consistently revealed a prevalence of vitamin D deficiency ranging between 70 and 100% across different age categories, with a pronounced impact observed in women aged 40 and above, contributing to post-menopausal bone density reduction.¹² In a study conducted in Patna, India on 192 apparently healthy post-menopausal women, it was noted that 53.13% population had vitamin D deficiency.¹¹ In a manner akin to this, a cross-sectional study was conducted within a community, involving 194 women aged 40 years or older residing in the village of Singur in West Bengal. Results showed that 19.6% of subjects were vitamin D deficient and 51.0% had insufficient vitamin D levels.¹³ Further, Tandon et al. also reported that 53.35% of the selected post-menopausal population had vitamin D deficiency.¹⁴

In a recent study conducted in Egypt, 52.4% of the post-menopausal women visiting a selected hospital were detected to be vitamin D insufficient (20–29.99 ng/mL).⁸ In a nationwide, multicentral study to explore Vitamin D deficiency in China, it was observed that 61.3% of the selected population was vitamin D deficient. There was a marked disparity in the prevalence of vitamin D deficiency, with urban residents exhibiting a notably higher incidence (64.9%) compared to their rural counterparts (57.7%).¹⁵

Effect of Vitamin D Deficiency in Post-Menopausal Women

Vitamin D inadequacy results not only in skeletal ailments but also in extra-skeletal disorders. This worldwide problem is projected to dramatically add to the massive load on the healthcare infrastructure due to its wide-ranging effects on health.

Skeletal Disorders

Osteoporosis is a degenerative condition of the bones characterised by bone mass loss and deterioration of the bone's microarchitecture, resulting in weakened bones and fractures. This condition is inexorably linked to inadequate vitamin D, which is the maximum widespread nutrient deficiency worldwide. The most significant bone loss predominantly occurs during the perimenopausal period and is correlated with a deficiency in oestrogen.¹⁶

Maintaining adequate vitamin D consumption is

recommended for the treatment of postmenopausal osteoporosis and bone loss. Vitamin D deficiency impairs calcium absorption, muscle strength, and balance, as well as bone mineralisation, potentially increasing the risk of falling.¹⁷ In a study by Suganthan et al., only 36.2% (95% CI: 27-45) of 105 post-menopausal women at the Endocrine Unit, Teaching Hospital Jaffna, had appropriate 25(OH)-D (25-hydroxyvitamin D) levels in serum, while 44% had insufficient levels, and 19% (95% CI: 12-27) of post-menopausal women had a deficiency. Bone pain, paraesthesia, malaise, easy fatigability, and muscle cramps were the symptoms of vitamin D deficiency that were frequently described. Thirty-eight per cent of the 71 participants who underwent a bone density assessment demonstrated osteoporosis. There was a notable correlation observed between the 25(OH)-D level and the spinal Z score.¹⁸

Vitamin D is crucial for the musculoskeletal system to function optimally because it enhances dietary calcium absorption, promotes the mineralisation of the osteoid, and regulates bone turnover and muscle function. From a biochemical perspective, an inadequate amount of vitamin D is associated with an increase in the concentration of blood parathyroid hormone (PTH), resulting in adverse effects stemming from vitamin D insufficiency. A study conducted in Romania involving 123 post-menopausal women to investigate the connection between vitamin D status and secondary hyperparathyroidism revealed that a significant majority had vitamin D deficiency with plasma 25(OH)-D value < 30 ng/mL. Consequently, these women are at risk of stress fractures due to the inverse relationship between 25(OH)D concentration and PTH, as well as alkaline phosphatase (ALP).¹⁹

In a transverse study on 190 post-menopausal osteoporotic women, deficiency of vitamin D was recorded in two-thirds of the patients. There was a statistically significant association observed between body mass index (BMI) and bone mineral density (BMD) at the lumbar spine. Addressing the challenge of reducing the incidence of osteoporosis, as well as minimising fractures and falls in post-menopausal women, hinges on proactive measures such as the prevention and early detection of vitamin D deficiency, sufficient calcium intake, and the implementation of diverse exercise routines.^{20,21}

Pelvic Floor Disorders

The complex female pelvic floor supports the abdominal cavity and the viscera of the pelvis through delicate interactions between its muscular connections to the pelvic bones. Faecal incontinence, pelvic organ prolapse, urine incontinence, and other issues with lower urinary and gastrointestinal tract storage and emptying are all examples of pelvic floor disorders. Women who have symptoms of

pelvic floor disorder (PFD) are clinically shown to have weak pelvic floor muscles. As vitamin D is vital for the efficient functioning of skeletal muscles, its insufficient level in serum may impact pelvic floor muscles. Since the detrusor wall contains a receptor for vitamin D, inadequate levels may also affect bladder function.²²

According to a study by Oberg et al. on 297 post-menopausal women from Norway, the presence of lower urinary tract symptoms (LUTS), including nocturia, urinary incontinence, and urgency, was prevalent, and these symptoms exhibited an inverse association with both vitamin D intake and vitamin D status. Women who received a bi-weekly dosage of 20,000 IU of vitamin D reported improvements in their lower urinary tract symptoms (LUTS).²³

In a randomised controlled trial, a total of 200 geriatric female patients aged between 65 and 78 were divided into two groups: a test group and a control group, each consisting of 100 selected participants. Detailed gynaecological, pregnancy, and clinical histories were collected from all participants. It was observed that there was a noticeable increasing trend in vitamin D deficiency as the number of years following menopause increased ($p = 0.1193$). Moreover, there was an improvement in the Mean Modified Vaginal Health Index (MVHI) associated with higher levels of serum vitamin D. The test group also demonstrated a significant association between urinary incontinence and mean vitamin D values. Further, MVHI rose significantly at follow-up studies conducted after 3 and 6 months of supplementation.²⁴

In a separate research investigation aimed at examining the correlation between vitamin D status and disorders of the pelvic floor (PFD), a cohort of 120 post-menopausal women coming to a tertiary care centre in South India, was studied. It was observed that 77.5% of women were deficient in vitamin D. The study further revealed that women with PFD had considerably lesser vitamin D levels as compared to women without PFD. Given vitamin D's significant role in neuromuscular function, muscle strength, and postural stability, it is justifiable to propose that vitamin D plays a crucial role in sustaining the function of pelvic floor muscles and, consequently, its involvement in the preclusion of PFD is a reasonable consideration.²⁵

Metabolic Syndrome

An assemblage of grave heart disease-causing factors: elevated fasting glucose, diabetes, central obesity, raised cholesterol and hypertension, metabolic syndrome (MS), is the fastest-growing non-communicable disease in the present-day world. The incidence of MS surges with menopause and may somewhat elucidate the evident increase of rate in cardiovascular diseases (CVD) post-menopause.²⁶ Owing to hormonal changes like a fall in

estrogen levels and a rise in androgens, a variety of lipid metabolic disorders emerge. Changes in lipid metabolism lead to the formation of superfluous fatty acids, cytokines, adipocytokines, and reactive oxygen species, causing dyslipidaemia, higher peroxidation of lipids, abdominal adiposity and insulin resistance.²⁷ The main risk factors for MS are socioeconomic status, less physical activity, growing urbanisation, genetic predisposition, vitamin D inadequacy, and consumption of ultra-processed foods and high-fat, sugar and salt (HFSS) foods. Decreased plasma concentration of 25(OH)D is correlated with chronic vascular inflammation, obesity, hypertension, diabetes, MS, and other conditions that are risk factors for CVD.²⁶

In a cross-sectional study conducted in Jeddah, Saudi Arabia, a total of 173 post-menopausal women aged 50 years or older with Type 2 Diabetes (T2D) were randomly selected for anthropometric assessments and fasting blood sample analysis. Notably, the levels of 25(OH)D exhibited an inverse association with fasting blood sugar, insulin, HOMA2-IR C-peptide (a marker of insulin resistance) and C-peptide. Additionally, serum 25(OH)D displayed a negative correlation with body weight and with measurements of hip and waist circumferences.²⁸ Similar to this, in another study aimed at assessing the status of vitamin D among selected post-menopausal populations and its connection with anthropometric parameters, it was found that 68% of the sample population had insufficient levels of 25(OH)D. Importantly, these inadequate 25(OH)D levels were inversely linked to metrics such as body fat mass, body mass index (BMI), arm circumference and hip circumference.²⁹

A total of 192 women diagnosed with T2D, encompassing both pre-menopausal and post-menopausal individuals, were subjects of investigation to assess their vitamin D status and its correlation with glycaemic control. Overall, 92.2% of women had inadequate vitamin D status with higher prevalence in post-menopausal T2D subjects. Further, only in post-menopausal women did hypovitaminosis D strongly correlate with insulin, HbA1c, and fasting blood glucose (FBG).⁷

Similarly in a separate cross-sectional investigation among 222 rural post-menopausal women in West Bengal, India, metabolic syndrome was noted in 46% of the selected subjects. Vitamin D insufficiency and deficiency affected 22% and 53% of MS-afflicted women respectively. Among the selected group, 47% with waist circumference more than or equal to 80 cm; 62% with fasting blood glucose more than or equal to 110 mg/dL; 54% with serum triglycerides (TG) more than or equal to 150 mg/dL; 51% with HDLC less than 50 mg/dL, 55% with BP more than or equal to 130/85 mm of Hg respectively showed vitamin D inadequacy. An inverse relationship was noted between fasting blood glucose (FBG) and the level of 25(OH)D.²⁶ According to

another larger, cross-sectional research including post-menopausal Korean women (n = 778), those with 25(OH)D levels between 4.2–9.7 ng/mL had a significantly greater risk of developing MS. Reduced value of blood 25(OH)D was also linked to high TG levels and raised blood pressure.³⁰ Similar associations between the group with the highest quartile of serum 25(OH)D levels and parameters such as blood pressure and serum triglycerides were reported among Korean post-menopausal women in another study.³¹

Further, to understand the long-term connection between vitamin D levels and cardiovascular outcome, healthy, post-menopausal women (n = 2016) inducted in the Danish Osteoporosis Prevention Study were followed up for 16 years. Among the group of women deficient in vitamin D (n = 788), there was a greater presence of cardiovascular risk factors compared to women who had sufficient vitamin D levels (n = 1225). Low levels of 25(OH)D were notably associated with higher body mass index (BMI), increased serum triglyceride levels, and lower levels of high-density lipoprotein (HDL) in the bloodstream.³²

However, in a research study of post-menopausal women from Bareilly, India, Sinha et al. noted a high (70.4%) pervasiveness of vitamin D inadequacy among women in mid-life but no relation between hypovitaminosis D and FBG was observed.³³ Likewise, in a separate research endeavour involving post-menopausal women, the authors did not identify a statistically significant connection between the presence of diabetes and vitamin D status, which in the authors' opinion could have been due to the small sample size.¹⁴

Sleep Disorders, Anxiety and Depression

As women age and undergo menopause, they are more susceptible to experiencing sleep problems compared to men. At perimenopause, the incidence of sleep problems ranges from 16 to 47%, which advances to 35 to 60% at post-menopause. Common symptoms associated with insomnia include mild depression and mood disorders, anxiety and mild depression.³⁴ Although a majority of women traverse menopause without any psychiatric issues, 20% of women are thought to experience depression. A lower incidence of depression in later years is linked to longer exposure to endogenous oestrogens, which translates into advanced age at menopause and an extended reproductive span.⁴ Stress, anxiety and depression are the most widespread psychological disorders amongst post-menopausal women.

In a multistage sampling transverse analytical study of 120 selected women (45–70 years), in Semnan (Iran), the levels of depression and anxiety were 22.5%, 13.3% and 1.7% in mild, moderate, and severe categories respectively; in addition, 20.8% women faced higher degrees of stress. Serum vitamin D had significant negative relationships with depression, anxiety, and stress.³⁵

In a research study involving post-menopausal women (n = 396) residing in specific urban and rural regions of Poland, the objective was to investigate the influence of vitamin D, serum thyroid stimulating hormone (TSH), and metabolic syndrome (MS) on the extent of depression. A negative correlation between depression severity and the serum TSH level was noted in the rural area residents. A higher depression severity was observed in the selected urban area residents with high blood pressure. Notably, there was no discernible association of the extent of depression with serum vitamin D levels or other criteria related to metabolic syndrome.³⁶

A chronic, recurrent condition, perimenopausal depression elevates the chance of self-harm and suicide. This condition not only has a negative impact on a person's health and everyday functioning, but it also places a heavy strain on their families and the wider community. Vasomotor symptoms are positively correlated with decreased ovarian oestrogen production, which is a high-risk factor for depression. There are several different symptoms associated with perimenopausal depression, and various perimenopause symptoms are also present during this time. The human brain contains many vitamin D receptors, and active vitamin D has antidepressant-like effects on the brain's dopamine system by protecting and regulating it. Consequently, there could be a negative correlation between the serum level of 25(OH)D and perimenopausal depression. Low serotonin levels are common in neuropsychiatric diseases, and vitamin D may be able to control them. In addition, according to Yuan et al., vitamin D may prevent depression by reducing inflammation and maintaining regular neural activity.³⁷

Cognitive Functions

Women who are perimenopausal or recently post-menopausal frequently complain of memory issues. The causal involvement of oestrogen in the cognitive impairments indicated by perimenopausal and recent post-menopausal women is supported by clinical trials describing the improvement of cognition with hormone replacement therapy (HRT). The transition to menopause may affect certain cognitive functions, such as verbal memory, attention and learning capacity, however, these functions have not been thoroughly studied. The apparent link between some women's cognitive issues and the menopausal transition raises the possibility that these issues are caused by menopausal hormonal changes. Cognitive issues may emerge from sleep disruption brought on by nocturnal hot flashes or from the consequences of the shifting hormonal environment in the areas of the brain that affect cognition.⁴ A randomised controlled trial was conducted, enrolling overweight or obese post-menopausal females having blood 25(OH)-D levels below

30 ng/mL, to explore the effects of vitamin D treatment on specific cognitive assessments in this population. Double-blinded randomisation was used to assign vitamin D3 supplementation at three different levels of 600, 2,000, or 4,000 IU/d for a period of one year. While the 2,000 IU/day set of participants outperformed the other sets in memory and learning tests ($p \leq 0.05$), a slower reaction time was observed in the 4,000 IU/day set than the 600 IU/day set. According to these findings, vitamin D affects cognition in different ways depending on the domain being measured. An increased dosage of vitamin D might also negatively affect reaction time.³⁸

In a study involving 170 post-menopausal women, subjects with significant 25(OH)D deficit had noticeably poorer results on the global cognitive performance index (NCI) ($p < 0.001$). Complex attention, cognitive flexibility, memory and executive functioning were all negatively impacted by extremely low 25(OH)D levels.³⁹

In another cross-sectional study, when compared to premenopausal women, post-menopausal women had significantly lower serum vitamin D levels (22.3 ng/mL vs 32.4 ng/mL; $p = 0.03$). Two measures of cognitive decline, ACE-R (Addenbrooke's Cognitive Examination – Revised) and MMSE (Mini-Mental State Examination), were found to have a substantial positive connection with blood levels of 25(OH)D in menopausal women.⁴⁰

Conclusion

Given a 70-year life expectancy on average, most women typically spend more than one-third of their lives past the menopausal transition. The susceptibility of post-menopausal women to vitamin D deficiency can be attributed to factors such as advancing age, changes in body composition, racial disparities, limited exposure to solar radiations, adiposity and insufficient vitamin D intake. Since menopause and vitamin D deficiency share several risk factors, such as impacts on bone health, metabolic functions, sleep patterns, and cognitive abilities, it is imperative for both peri-menopausal and post-menopausal women to uphold adequate vitamin D status. Generally, vitamin D-rich foods are few in number, expensive and mostly of animal origin, e.g. yolks, beef liver, red meat, oily fish, and fortified dairy items. Limited choice of foods rich in vitamin D makes compliance with dietary recommendations difficult. Hence, there is also a pressing need to explore alternatives like sun-exposed mushrooms and yeast containing the vitamin D2 form, which may add variety to the diet and are also suitable for populations following a vegetarian diet. Further, unambiguous public health policies and food fortification guidelines for vitamin D supplementation ought to be formulated and implemented which will help to boost the intake.

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