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MINI REVIEW ARTICLE

Association of Hypovitaminosis D with Metabolic Syndrome in Postmenopausal Women

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Abstract
The prevalence of vitamin D deficiency and metabolic syndrome is spreading like a pandemic globally; postmenopausal women are particularly vulnerable population. Hypovitaminosis D is reported to predispose to various components of metabolic syndrome like dyslipidemia, hypertension, diabetes and obesity. The purpose of this review is to highlight the recently published evidence, evaluating the association of vitamin D deficiency with metabolic syndrome in postmenopausal women. Besides, it emphasizes the long-term risks involved with low vitamin D levels and importance of vitamin D supplementation. Data were obtained from PubMed, Google Scholar and individual searches.

Keywords Vitamin D · Metabolic syndrome · Postmenopausal women · Insulin resistance · Obesity

Vitamin D: Synthesis, Metabolism and Association

Vitamin D, a fat-soluble vitamin, is also known as sunshine vitamin [1]. It is mainly synthesized endogenously in the skin, under ultraviolet (UV) B exposure, and is further activated by the liver and kidney. Foods like eggs, liver, cod liver oil, mushroom, etc., are also rich sources. The serum levels of 25(OH) D in the range of 30–50 ng/ml are considered to be optimum, whereas levels between 21 and 29 ng/ml indicate vitamin D insufficiency [2]. Vitamin D deficiency has been defined as level less than 20 ng/ml [2]. Various studies have established the association of low vitamin D levels with osteomalacia, secondary hyperparathyroidism, osteoporosis [1]. Vitamin D has also been shown to have an inverse association with diabetes, adiposity, dyslipidemia, hypertension and consequently metabolic syndrome (MS) and cardiovascular disease (CVD) events [3]. It is considered as the commonest medical condition and an important public health menace in the world [4].

Recent studies have reported an increase in vitamin D deficiency globally, as a pandemic [4]. The observed increase in vitamin D deficiency is due to changes in lifestyle like use of sunscreens and reduction in outdoor activities, socioeconomic transition and urbanization [5]. This fact is supported by the Korean National health and Nutrition Examination Survey who reported a high prevalence of hypovitaminosis D among South Korean postmenopausal women, although South Korea because of its location at latitudes 33°–38° receives adequate UVB light for vitamin D synthesis [5]. Similarly, Chon et al. [6] found that people with low physical activity, residing in urban areas, had significantly less proportion of people in high-serum vitamin D levels compared to those residing in rural areas, with more physical activity and working outdoors like farming and fishing.

Vitamin D Deficiency in Postmenopausal Women

Vitamin D deficiency is more prevalent in postmenopausal women owing to loss of estrogen and decreased capacity of absorption of sunlight and synthesis of 25 hydroxy vitamin D (25(OH) D) by the aged skin [7, 8]. Several studies from Indian and Western world have found the incidence ranging

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from 50 to 90% [6, 9]. Among the cohort of postmenopausal women residing in Jammu and Kashmir in Northern India, Vitamin D deficiency and insufficiency were found to be in 80% and 14.8%, respectively [1]. Similar results have been revealed in the study conducted in South India in postmenopausal women. In this study, 70% women were found to have Vitamin D deficiency, while Vitamin D insufficiency was revealed in 23% postmenopausal women [10]. Study on Han Chinese postmenopausal women found vitamin D deficiency in 31.2% and 50.6% were vitamin D insufficient [11]. This article highlights the recent evidence published concerning the association of vitamin D deficiency with metabolic syndrome in postmenopausal women.

Metabolic Syndrome in Postmenopausal Women

MS is a set of metabolic abnormalities including dyslipidemia; triglycerides (TG) ≥ 150 mg/dl, high-density lipoprotein–cholesterol (HDL-C) ≤ 50 mg/dl, waist circumference ≥ 88 cm, systolic blood pressure (SBP) ≥ 130 mmHg or diastolic blood pressure (DBP) ≥ 85 mmHg or on antihypertensive medication, fasting blood glucose ≥ 100 mg/dl or on treatment for type 2 diabetes [12]. Due to the association of metabolic syndrome and CVD, Indian epidemiologists and the WHO have been alerting on the rapidly rising burden of CVD; estimates predict that by the year 2020, CVD would be the major cause of death and disability in India [13]. Various definitions have been suggested for metabolic syndrome by World Health Organization (WHO), the European Group for the study of Insulin Resistance (EGIR), American Association of clinical Endocrinologists (AACE), Harmonized criteria (H-MS), International Diabetes Federation (IDF) and Modified National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III criteria). Out of these, the most commonly used is the NCEP III criteria. As per the NCEP ATP III criteria, the diagnosis of MS is made when three or more of the above-mentioned cofactors exist [12].

The transition from pre to postmenopause is associated with development of obesity, dyslipidemia and hyperglycemia attributed directly to ovarian failure or indirectly resulting from central fat redistribution with estrogen deficiency [14]. There is high prevalence of metabolic syndrome in postmenopausal women, and it increases with age, socioeconomic status, urbanization and lack of physical activity; no association of MS was found with education, parity, family history and age at menopause [15, 16]. Korean study found that the metabolic syndrome prevalence increased from 10.8 to 43.1% from a group of < 50 years to 65–69 years [6]. The overall prevalence of metabolic syndrome has been reported to be in the range from 16.8 to 65.7% and is mainly attributed to overweight and obesity in postmenopausal women [14, 15]. Among postmenopausal women participants from Gorgan, the reported prevalence of MS was 31% with maximum prevalence of dyslipidemia and high-waist circumference [17]. The study on 616 postmenopausal women from Han Chinese reported prevalence of metabolic syndrome to be 31.7% [11]. In a cohort of rural block of West Bengal, 46% postmenopausal women had metabolic syndrome [18]. Studies from Brazil and French population have reported prevalence to be 22.2% and 45.7%, respectively [19]. Studies have found that, approximately, 50% of female population in more than 50 years age are suffering from metabolic syndrome which is a potential risk factor for cardiovascular disease, the leading cause of mortality in postmenopausal women [18, 20, 21]. India has around 43 million menopausal women, and it is projected that by the year 2026, the menopausal population would increase to nearly 103 million [22]. These figures represent the national burden of MS and the possible risk of CVD and type 2 diabetes in this subset of women.

Metabolic Syndrome and Vitamin D

Vitamin D deficiency and obesity are proinflammatory states, have increased C reactive protein, fibrinogen, interleukin-6, tumor necrosis factor-α, etc. They contribute to insulin resistance and thereby lead to dyslipidemia, diabetes and metabolic syndrome [3]. Vitamin D deficiency and vitamin D insufficiency have been reported in 53% and 22% postmenopausal women with metabolic syndrome, respectively [18]. In Gorgan study, Vitamin D deficiency was found in 32.26% postmenopausal women with metabolic syndrome [17]. The presence of vitamin D receptors (VDR) in almost all the cells including vascular smooth muscle, endothelium and cardiomyocytes has proved its association with MS, obesity, diabetes and CVD [2].

The association of metabolic syndrome with hypovitaminosis in postmenopausal women remains controversial. Most of the studies have reported an inverse association of hypovitaminosis D with metabolic syndrome [8, 23, 24] but others have not [6, 7, 16–18, 25, 26]. The study by Huang et al. reported that with decreasing vitamin D levels, there was a significant increase in adjusted odds ratio (OR) for metabolic syndrome (P for trend 0.009). There was negative association of metabolic syndrome and its components with serum Vitamin D levels [11]. The study in 2012 showed no significant differences in serum levels of vitamin D among postmenopausal women with or without metabolic syndrome [17]. Mitra et al. [7] did study on 64 postmenopausal women and found that the proportion of subjects with vitamin D deficiency did not differ between the two groups of postmenopausal women, with MS or non-MS. The same was also reported by Alissa et al. [16]. Chon et al. [6] and

Mitra et al. [7] found no significant difference in prevalence of MS between different categories of vitamin D adequacy.

Several studies have reported association with all components of MS, i.e., increased TGs, cholesterol, body mass index (BMI), BP, fasting plasma glucose, insulin resistance, overweight, obesity and lower HDL-C levels in vitamin D deficient postmenopausal women [27]. However, few studies have observed association with only some components like TG [6, 16, 23], fasting plasma glucose [16] and BP [6, 16, 23]. Contrary to this, the study in 2012 showed no significant differences in parameters of metabolic syndrome among postmenopausal women with or without vitamin D deficiency [16]. Also, Mitra et al. [7] found no correlation between components of MS and serum vitamin D levels.

Components of MS and Vitamin D

Insulin Resistance, Hyperglycemia and Vitamin D

The vitamin D plays an important role in preserving the normal insulin metabolic function. The results of animal studies suggest that vitamin D has a genomic influence within islets of Langerhans and regulates insulin synthesis and secretion from pancreatic beta cells. This regulation is mediated by VDR expression in pancreatic beta cells secreting insulin and in target tissues like adipocytes and skeletal muscle. Hypovitaminosis D hinders conversion of proinsulin to insulin [2]. Experimental and epidemiological studies suggest an association of decreased levels of 25(OH)D with decreased levels of insulin release, increased prevalence of insulin resistance and type 2 diabetes in the elderly [24, 28]. A study in 2017 on West Bengal women found that plasma levels of 25(OH)D has statistically significant inverse association with fasting blood glucose ($p=0.01$) [18]. There was significant negative correlation ($p=0.02$) between fasting blood glucose and serum vitamin D levels [18]. A clinical comparative study calculated homeostasis model assessment of insulin resistance (HOMA-IR) and compared its levels in women with hypovitaminosis and normal vitamin D levels. Women with adequate Vitamin D levels had lower levels of HOMA-IR compared to those with hypovitaminosis D [8]. A study on Han Chinese women found negative correlation between serum vitamin D levels and fasting glucose, fasting insulin and HOMA-IR [11]. Fondjo et al. reported statistically significant increase in fasting glucose, HbA1C and HOMA-IR in postmenopausal vitamin D deficient group compared to vitamin D non-deficient group [29].

Dyslipidemia and Vitamin D

Several studies suggest an inverse association of vitamin D levels with dyslipidemia and obesity [1, 16, 27, 30]. Chon et al. [6] in his study on 4364 Korean postmenopausal women observed statistically significant decrease in the individual components of metabolic syndrome with increasing serum vitamin D levels. They reported a statistically significant association of decrease in prevalence of elevated TGs and low HDL-C with higher serum levels of 25(OH) D ($p=0.014$ and 0.002 respectively) [6]. With an increase in tertiles of serum levels of 25(OH)D, there was decrease in odds ratio trend for the prevalence of increase TGs and reduced HDL-C (p for trends $=0.043$ and 0.010, respectively) [6]. Schmitt et al. reported increased cholesterol and triglycerides in women with hypovitaminosis D ($p<0.05$) [8]. Huang et al. [11] found negative association of vitamin D levels with TGs and positive association with HDL-C. Branco et al. in 2019 reported negative correlation of TG with vitamin D levels in postmenopausal women with type 2 diabetes [31]. Srimani et al. [18]found that median 25 (OH) D level decreased with increase in triglyceride levels and also median vitamin D level decreased with decrease in HDL cholesterol level, but there was no significant difference.

Hypertension and Vitamin D

The association between hypovitaminosis D and hypertension was studied among postmenopausal women in West Bengal. They found an insignificant inverse association of serum 25(OH)D with systolic and diastolic blood pressure [18]. However, a statistically significant association between elevated blood pressure and vitamin D was observed in Korean study ($p=0.020$) [6]. With increasing serum levels of serum 25(OH)D, the OR for prevalence of elevated blood pressure showed a decreasing trend (p for trend $=0.066$) [6]. The absence of vitamin D receptors activation leads to decreased suppression of rennin angiotensin system and ultimately leads to hypertension [32]. Huang et al. [11] reported negative association of serum 25(OH)D level with systolic and diastolic blood pressure.

Obesity and Vitamin D

Studies have reported an inverse association between obesity, waist circumference and serum levels of vitamin D [1, 16, 18, 30]. With decrease in 25(OH)D levels, there was increase in waist circumference and prevalence of abdominal obesity among Korean postmenopausal women [6]. Joshi et al. found a statistically significant association of low serum levels of vitamin D with high BMI ($p\leq0.02$). They concluded that vitamin D deficiency is associated with obesity as vitamin D synthesized in the skin is sequestered by the subcutaneous fat leading to low circulating levels of vitamin D [1]. Srimani et al. [18] did study in a rural block of West Bengal and found significant increase in median 25(OH)D level among subjects with waist circumference <80 cm to >80 cm.

Vitamin D Supplementation

There are very scarce studies on vitamin D supplementation in postmenopausal women. The review article in 2019 concluded that vitamin D supplementation with cholecalciferol and calcifediol can maintain sufficient vitamin D levels in postmenopausal women. They concluded that maintaining adequate vitamin D levels could improve metabolic variables in postmenopausal women [33]. A recent study gave vitamin D supplements of 1000 IU vitamin D3 to postmenopausal women for 9 months and reported reduction in MS risk profile in women with vitamin D deficiency [2]. After 9 months of treatment, they found reduction in blood insulin levels (− 13.7%), decrease in blood triglyceride levels (− 12.2%) and HOMA-IR (− 17.9%). However, the authors did not observe any change in blood pressure and anthropometric measures. They proposed that to see the effect of vitamin D supplementation on anthropometric measures, there needs to be a long-term vitamin D supplementation. Contrary to this study, another study done on 305 postmenopausal women reported no change in cholesterol, TG, HDL and insulin levels after daily supplementation with 1000 IU vitamin D [34]. Bentes et al. [35] review article included five clinical trials and concluded that vitamin D supplementation alone, with doses of less than 1000 IU/day, can only increase serum vitamin D levels with no significant increase in physical fitness levels of postmenopausal women with metabolic disorders.

Conclusion

The association of hypovitaminosis D with metabolic syndrome in postmenopausal women remains controversial. Although most of the evidence suggests that postmenopausal women with hypovitaminosis D are at a greater risk of developing metabolic syndrome compared to those with normal levels. However, some studies suggest an insignificant association. Some studies suggest significant association of low vitamin D levels with some of the components of metabolic syndrome. The authors recommend that interventions to maintain adequate serum levels of 25(OH) D in postmenopausal women may decrease risk of metabolic syndrome and its components and ultimately reduce cardiovascular events and mortality. Further randomized trials and research is required to give appropriate guidelines to prevent hypovitaminosis D and establish association of vitamin D deficiency with metabolic syndrome and its components. This would reduce long-term morbidity and mortality among postmenopausal women.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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