«Vitamin D hypovitaminosis as a risk factor for metabolic syndrome in menopausal women»

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The climacteric period is a key stage in a woman's life, representing a physiological transition during which there is a gradual decline in ovarian activity. At this time, women often develop menopausal metabolic syndrome, manifested by an increase in visceral fat mass, insulin resistance and hyperinsulinaemia, which leads to disorders of carbohydrate, viride and purine metabolism. The role of vitamin D in postmenopausal women remains poorly understood. It is noteworthy that hypovitaminosis D is more common in postmenopausal women compared to premenopausal women. This paper reviews the factors contributing to menopausal metabolic syndrome and its associated risks. The relationship and impact of menopausal metabolic syndrome on vitamin D deficiency is also described.

Key words: *menopausal symptoms, menopause, metabolic syndrome, 25-hydroxyvitamin D, vitamin D deficiency.*

Metabolic syndrome (MS) is a complex of metabolic disorders including visceral obesity, carbohydrate intolerance, dyslipidaemia, arterial hypertension and insulin resistance [6]. Risk factors for MS include advanced age, alcohol consumption, smoking, heredity, and sedentary lifestyle [13].

Postmenopausal women tend to have increased fat deposits on the flanks and abdomen, which is one of the risk factors for the development of MS [14]. It has been observed that menopausal transition and postmenopausal period also contribute to the increased risk of MS as they are associated with decreased estrogen levels and

increased likelihood of insulin resistance [19, 22]. According to the literature, increased body weight in postmenopausal women increases the incidence of vasomotor symptoms. Researchers identify obesity as one of the main components of MS and note the association between abdominal obesity and hot flashes that negatively affect the cardiovascular system [12].

The prevalence of vitamin D deficiency in the general population ranges from 20 to 90% depending on serum 25-hydroxyvitamin D (25(OH)D) levels [22]. Because there are no uniform clinical guidelines for the diagnosis of vitamin D deficiency, hypovitaminosis D is defined as serum 25(OH)D levels below 30 nmol/L, 50 nmol/L, or 75 nmol/L [3, 5, 12].

The Institute of Medicine recommends a daily intake of 600 IU of vitamin D for adults under 70 years of age and 800 IU for those over 70 years of age [18]. According to Endocrine Society recommendations, age categories 19-70 years and over 70 years should follow the same vitamin D intake rates: at least 600 IU and 800 IU per day, respectively. In addition, for adults with vitamin D deficiency, it is recommended to take 50,000 IU per week for 8 weeks and then 1500-2000 IU per day for prophylaxis [12]. Vitamin D plays an important role in maintaining calcium and phosphorus homeostasis and in normalising bone metabolism [10]. However, its effects go beyond bone metabolism. Recent studies have linked hypovitaminosis D to various non-communicable diseases such as metabolic syndrome, diabetes, some cancers and psychiatric disorders [21-23]. Studies on the association between vitamin D and metabolic syndrome in postmenopausal women are quite rare [20], and there are no systematic reviews on this topic. The aim of our review was to summarise the current evidence, especially recent studies, on the relationship between hypovitaminosis D and metabolic syndrome in postmenopausal women.

Research articles were searched in PubMed, Cochrane, SCOPUS and Embase databases to ensure high informativeness on the topic under study. Studies published between 2011 and August 2023 were included in the review, as prior to 2011.

Our search identified 63 articles, of which 49 were excluded for various reasons (duplicates, discussion results, study design, and failure to meet inclusion criteria). This descriptive review is based on 10 cross-sectional studies and one randomised controlled trial (RCT). Menopausal period is defined as the absence of a menstrual cycle for 12 months or more. In all studies, serum 25(OH)D concentration was used to assess vitamin D status. Because serum 25(OH)D has a longer half-life and reflects both dietary vitamin D and endogenously synthesised vitamin D in the skin, it is the most common biomarker of vitamin D status. In all studies (except one), vitamin D deficiency was defined as serum 25(OH)D levels below 50 nmol/L. Individual manifestations of metabolic syndrome were assessed at baseline and endpoint for both groups.

This review analysed 11 studies on the association between serum vitamin D levels and metabolic syndrome (MS) in postmenopausal women. One 2019 study found that postmenopausal women receiving 1000 IU/day of vitamin D had more favourable trends in laboratory parameters associated with metabolic syndrome compared with a control group taking placebo.

In this randomised controlled trial (RCT), 160 participants were divided into two groups: the first group received vitamin D at a dose of 31000 IU/day, while the control group took placebo for 9 months. Multivariate adjusted analyses revealed that women who took vitamin D3 had a significantly lower risk of developing metabolic syndrome (odds ratio (OR), 0.42; 95% confidence interval (CI), 0.21-0.83), hypertriglyceridaemia (OR, 0.43; 95% CI, 0.22-0.85) and hyperglycaemia (OR, 0.23; 95% CI, 0.10-0.52), compared with women in the placebo group. However, no

differences in blood pressure and anthropometric parameters were recorded between the groups.

In a cross-sectional study, postmenopausal women with hypovitaminosis D were found to have a higher prevalence of metabolic syndrome (MS), hypertriglyceridaemia and low HDL-cholesterol compared to postmenopausal women with normal vitamin D levels.

In another study including 340 postmenopausal women, vitamin D deficiency was shown to increase the risk of metabolic syndrome, hypertriglyceridaemia and obesity. Also in this study, serum 25(OH)D levels were found to be lower in women with metabolic syndrome compared to those without the syndrome. Additional studies have noted an association between serum 25(OH)D levels and metabolic syndrome

The association between serum levels of 25(OH)D and various cardiometabolic risk factors as well as metabolic syndrome (MS) was investigated in 64 postmenopausal women. Results showed no significant differences in cardiometabolic risk profiles between women with deficient and adequate vitamin D levels. Women with and without MS had comparable serum 25(OH)D levels. Insulin resistance was not assessed in this study, which could provide a clearer picture of the possible association between the high prevalence of hypovitaminosis D and metabolic syndrome.

The results of a study involving 616 postmenopausal women suggest a synergistic effect of vitamin D and estradiol deficiency on the severity of metabolic syndrome. A direct relationship was found between serum 25(OH)D levels and estradiol concentrations. The researchers noted that increased 25(OH)D levels were associated with lower blood pressure, normalisation of lipid profile and blood glucose levels. After multivariate analysis, the odds ratio (OR) for MI was 2.19 (95% confidence interval (CI), 1.19-4.01; $p<0.009$) for women with vitamin D deficiency compared with

those with sufficient levels. This association persisted even after adjustment for estradiol concentration.

A recent study demonstrated that the combination of aerobic exercise and intake of 50,000 IU of vitamin D per day significantly reduced levels of inflammatory markers such as C-reactive protein and interleukin-6, and improved all measures of metabolic syndrome in postmenopausal women. Overall, evidence from cross-sectional studies suggests that hypovitaminosis D is associated with an increased risk of MS in postmenopausal women.

New studies confirm that vitamin D plays an important role in various noncalcaemic functions. Vitamin D receptors (VDRs) have been found in a number of insulin-independent cells and tissues such as liver, skeletal muscle and adipose tissue, indicating that vitamin D is involved in glucose utilisation, insulin secretion and insulin sensitivity. Overweight, obesity (especially abdominal obesity) and metabolic syndrome were associated with lower serum 25(OH)D levels. Hypovitaminosis D is associated with increased systolic blood pressure, lower HDL cholesterol levels, and insulin resistance.

Vitamin D deficiency plays a significant role in the pathogenesis of type 2 diabetes (T2D) by increasing insulin resistance and promoting inflammation. Polymorphisms in vitamin D receptor (VDR) genes are associated with alterations in insulin secretion and insulin sensitivity. Vitamin D receptors are found both in insulin-secreting pancreatic β-cells and in 1α-hydroxylase, which converts circulating 25(OH)D into active 1,25-dihydroxyvitamin D (1,25(OH)2D). The effects of insulin may occur through decreased insulin receptor expression or impaired insulin receptor signalling flow. Vitamin D stimulates insulin receptor expression in peripheral tissues, thereby increasing glucose uptake. Since insulin-mediated intracellular processes are calcium-

dependent, vitamin D may indirectly influence insulin sensitivity in skeletal muscle and adipose tissue.

An inverse relationship between serum 25(OH)D levels and triglyceride concentrations in postmenopausal women has also been observed. This association may be due to decreased intestinal absorption, reduced lipid synthesis and reduced lipolysis. A meta-analysis of randomised controlled trials demonstrated a positive association between 25(OH)D levels and HDL cholesterol, suggesting that hypovitaminosis D may be responsible for the reduction in LDL cholesterol.тHypovitaminosis D may also contribute to an atherogenic lipid profile, which is considered a major risk factor for coronary heart disease. The direct relationship between serum levels of 25(OH)D and apolipoprotein A-1 suggests a possible role of vitamin D in the formation of HDL particles in blood. In addition, it has been hypothesised that vitamin D receptors regulate cholesterol concentration by increasing the synthesis of bile acids from cholesterol.

Vitamin D affects lipid metabolism by inhibiting adipogenic transcription factors and limiting lipid accumulation during adipocyte differentiation. Vitamin D metabolites promote the production of adipokines and activate the inflammatory response in adipose tissue, which may cause disturbances in normal adipose tissue metabolism in hypovitaminosis D. Because adipose tissue plays an important role in the regulation of energy balance, lipid metabolism, and inflammation, serum 25(OH)D levels are of significant importance in maintaining metabolic health. Several studies have found an inverse relationship between serum 25(OH)D levels and measures such as obesity, body weight and body mass index (BMI). This association is likely due to the sequestration of vitamin D in adipose tissue, resulting in a decrease in serum levels. As mentioned earlier, diet may influence the interaction between vitamin D and the risk of metabolic syndrome (MS). It has been observed that postmenopausal women often have low protein intake, which increases the risk of developing MS. The metabolic

disturbances commonly seen in postmenopausal women cannot be attributed solely to vitamin D deficiency. This group of women typically has older age and less physical activity, which reduces sun exposure and contributes to vitamin D deficiency. Also, decreased physical activity is associated with an increased risk of obesity. Due to hormonal changes that occur with age, postmenopausal women tend to have unfavourable biomarkers of body composition such as increased fat mass. High-protein diets (usually low in carbohydrates) have been associated with reductions in body weight, fat mass, triglycerides, and blood pressure, which are important components of metabolic syndrome.

Vitamin D, estrogen and metabolic syndrome (MS) are interrelated. The binding of $1,25(OH)_2D$ to vitamin D receptors (VDRs) initiates the genetic expression of enzymes responsible for the conversion of androgens and estrogens into their active forms. One of these enzymes is 17β-hydroxysteroid dehydrogenase, which regulates the concentration of intracellular steroid hormones in target tissues. Aromatase, which is responsible for estrogen synthesis, has various functions in tissues such as ovaries, mammary glands and adipose tissue. Studies show that vitamin D deficiency may be associated with various reproductive disorders in women, including subfertility, polycystic ovarian syndrome and endometriosis. Thus, it is conceivable that hypovitaminosis D in postmenopausal women may exacerbate the metabolic syndrome. At the same time, it remains unclear whether increasing 25(OH)D levels can reduce the impact of MS biomarkers and reduce the risk of cardiovascular disease in postmenopausal women.

The studies analysed have several strengths. Many cover a large sample, allowing their results to be applied to a wider population. However, longitudinal studies and randomised controlled trials (RCTs) are needed to further explore the association between components of the metabolic syndrome and hypovitaminosis D in postmenopausal women. It should be noted that most of the studies reviewed are cross-

sectional and no definite conclusions about causal relationships can be drawn. However, it is unclear how not accounting for sun exposure affected the association between serum vitamin D and cardiovascular disease in postmenopausal women. In these studies, the estimation of vitamin D levels was based on a single serum measurement, which may not reflect the actual concentration of vitamin D in the body over time. The results of studies with small samples are difficult to generalise to the whole population. The studies reviewed are also heterogeneous and differ in the way they categorise deficiency, insufficiency and normal vitamin D levels. They were conducted in different countries, with varying sample sizes and study methods. Therefore, the results of these studies cannot be generalised to postmenopausal women worldwide, including Uzbekistan in particular. It is important to focus on improving vitamin D status in postmenopausal women by recommending the inclusion of fish and vitamin D-rich foods in the diet. As dietary sources of vitamin D are very limited, there may be a desire to resort to supplementation to increase vitamin D intake. Although the safety of vitamin D at low doses is well documented, the safety of higher doses remains uncertain. Therefore, postmenopausal women are advised to consult with medical professionals before starting supplements containing more than 4,000 IU/day (the maximum tolerated amount), although many health experts consider intake of up to 10,000 IU/day to be safe. Caution should be used when recommending high doses of vitamin D due to possible, albeit rare, health risks such as kidney stone formation, soft tissue calcification, hypercalcaemia, gastrointestinal symptoms, altered mental status and increased blood pressure. Due to these potential adverse effects, treatment of vitamin D deficiency should only be done under the supervision of a physician.

In summary, most studies indicate an inverse association between serum 25(OH)D levels and metabolic syndrome (MS) in postmenopausal women. Currently, there are no data to accurately determine the optimal serum 25(OH)D concentration or dietary vitamin D intake level at which a health benefit is observed in postmenopausal women.

Controlled studies are needed to elucidate the extent to which improved vitamin D status may reduce MS-related pathologies in this group of women. In addition, the exact mechanism of action of vitamin D requires further clarification.

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