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# Deficiency of vitamin d in patient with primary hypothyroidism and as related risk factor for cardiovascular diseases

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## **Abstract**

Hypothyroidism is believed to be associated with dyslipidemia and is considered a risk factor for the development of atherosclerotic cardiovascular diseases (ASCVD). Vitamin D, due to its steroid hormone action, retains cell function and controls the metabolism of lipids. Therefore, the present study was carried out to show the association of the risk factors of ASCVD. Cardiovascular disease (CVD) is caused by both clinical and subclinical hypothyroidism by disrupting healthy endothelial function by various mechanisms such as inflammation, triggering lipid disorders and oxidative stress. In the present study, a strong correlation was observed between increasing TSH and the parameters of lipid profile. Hypothyroidism and hypovitaminosis D are known as independent risk factors for the development of cardiovascular diseases. Hypothyroidism and hypovitaminosis D are associated and correlated with total cholesterol, triglycerides, and low-density lipoprotein in Saudi patients. It is also recommended that vitamin D deficiency be checked in hypothyroid patients and that appropriate supplementation may be given if needed. Furthermore, for early detection and/or prediction of cardiovascular disease, screening of thyroid hormone and vitamin D levels should be undertaken at an early stage.

## **Introduction**

- Vitamin D deficiency(1) is a global health problem, its role as an immune modulator has been recently emphasized. The evidence is increasingly pointing towards vitamin D significant role in reducing the incidence of autoimmune diseases. However, at this time the research on its role in autoimmune and thyroid disease is not conclusive.

- We aimed to examine the relationship between hypothyroidism and vitamin D deficiency and to clarify the relation between serum calcium levels with hypothyroid disease.(2)
- Nowadays one may encounter an increasing number of reports on the relationships between vitamin D deficiency and the risk of a number of systemic and organ diseases outside the bone system. Emphasized is especially its role in autoimmune(1) and oncological diseases and diabetes mellitus (2)(3), the importance of physiological saturation with vitamin D for normal fetal development during pregnancy and further postnatal life , the effects of vitamin D on the aging including mortality and its association with mental health. In this review we tried to summarize and discuss recent opinions on the possible role of vitamin D in the risk of thyroid diseases development, as the most frequent endocrinopathies.

### **vitamin D deficiency**

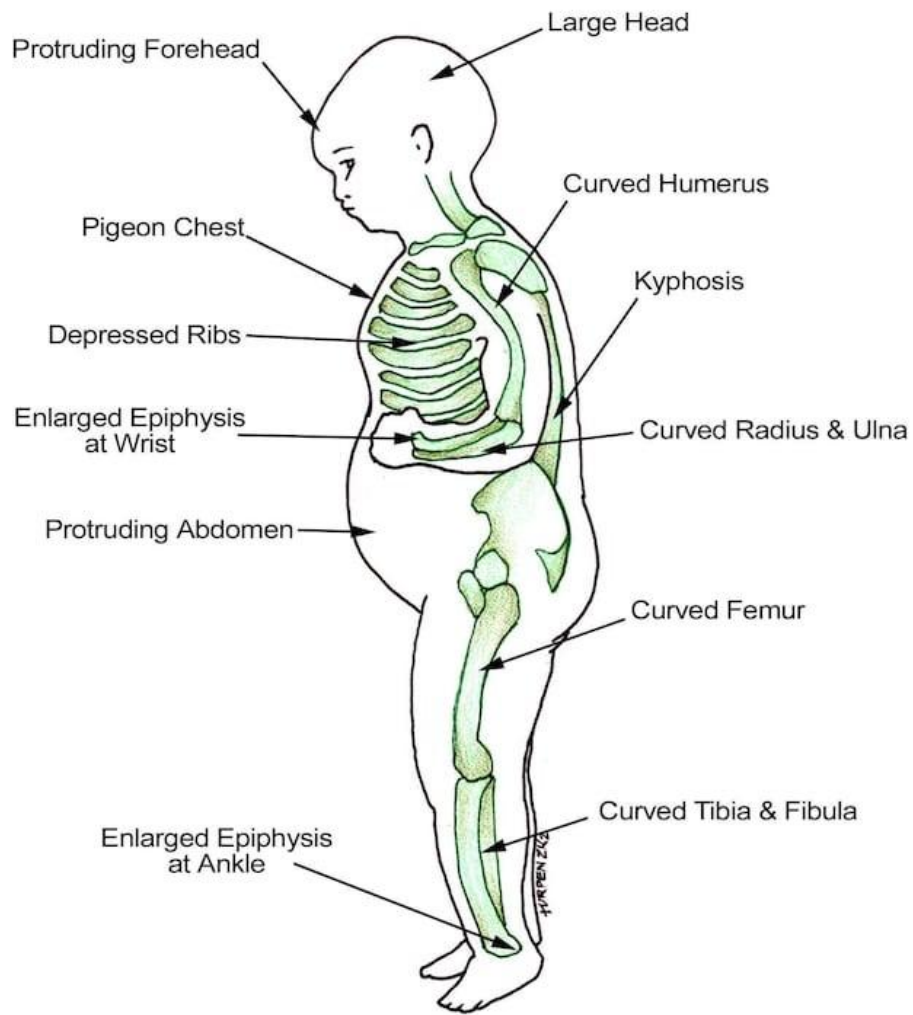
is defined by most experts as a 25-hydroxyvitamin D level of less than 20 ng per milliliter (50 nmol per liter).7-10 25-Hydroxyvitamin D levels are inversely associated with parathyroid hormone levels until the former reach 30 to 40 ng per milliliter (75 to 100 nmol per liter), at which point parathyroid hormone levels begin to level off (at their nadir).10-12 Furthermore, intestinal calcium transport increased by 45 to 65% in women when 25-hydroxyvitamin D levels were increased from an average of 20 to 32 ng per milliliter (50 to 80 nmol per liter). Given such data, a level of 25-hydroxyvitamin D of 21 to 29 ng per milliliter (52 to 72 nmol per liter) can be considered to indicate a relative insufficiency of vitamin D, and a level of 30 ng per milliliter or greater can be

considered to indicate sufficient vitamin D. Vitamin D intoxication is observed when serum levels of 25-hydroxyvitamin D are greater than 150 ng per milliliter (374 nmol per liter).

With the use of such definitions, it has been estimated that 1 billion people worldwide have vitamin D deficiency or insufficiency. According to several studies, 40 to 100% of U.S. and European elderly men and women still living in the community are deficient in vitamin D.

More than 50% of postmenopausal women taking medication for osteoporosis had suboptimal levels of 25-hydroxyvitamin D.

So Vitamin D deficiency(4)(5) can result from inadequate exposure to sunlight; malabsorption; accelerated catabolism from certain medications; and, in infants, the minimal amount of vitamin D found in breast milk. In children, vitamin D deficiency can result in rickets, which presents as bowing of the legs; in adults, it results in osteomalacia, which presents as a poorly mineralized skeletal matrix.



## Etiology

Vitamin D deficiency can result from the following:

Inadequate exposure to sunlight - This causes a deficiency in cutaneously synthesized vitamin D; adults in nursing homes or health care institutions are at a particularly high risk.(6)

Vitamin D malabsorption problems - People who have undergone resection of the small intestine are at risk for this condition; diseases associated with vitamin

D malabsorption include celiac sprue, short bowel syndrome,(7) and cystic fibrosis.(8)

Minimal amounts of vitamin D in human breast milk - The American Academy of Pediatrics recommends vitamin D supplementation starting at age 2 months for infants fed exclusively with breast milk.

Medications - Some medications are associated with vitamin D deficiency; drugs such as Dilantin, phenobarbital, and rifampin can induce hepatic p450 enzymes to accelerate the catabolism of vitamin D.

### **Signs and symptoms**

Vitamin D deficiency is often clinically silent. Manifestations are as follows:(3)(5)

\_Children are often found to have started walking late or prefer to sit down for prolonged periods

\_Adults can experience chronic muscle aches and pains

Physical findings in severe vitamin D deficiency are as follows:

\_In children, bowing in the legs

\_In adults, periosteal bone pain, best detected with firm pressure on the sternum or tibia

## **Diagnosis**

Measurement of serum 25-hydroxyvitamin D (25[OH]D) is the best test to determine vitamin D status. Levels of 25(OH)D are interpreted as follows[1]

\_ 21-29 ng/mL (52.5-72.5 nmol/L): Vitamin D insufficiency

\_ < 20 ng/mL (< 50 nmol/L): Vitamin D deficiency

Screening for vitamin D deficiency is recommended only in those individuals who are at high risk for vitamin D deficiency, including the following[2]

1. Patients with osteoporosis
2. Patients with a malabsorption syndrome
3. Black and Hispanic individuals
4. Obese persons (body mass index >30 kg/m<sup>2</sup>)[3]
5. Patients with disorders that affect the metabolism of vitamin D and phosphate (eg, chronic kidney disease)

## **Prevention and Treatment**

To prevent vitamin D deficiency(9) (10) in persons with inadequate sun exposure, the Institute of Medicine has recommended adequate intake (AI) based on levels needed to maintain optimal bone health in all members of a healthy population(11). The current daily AI is 200 IU for infants, children, and adults younger than 51 years; 400 IU for adults 51 to 70 years of age; and 600 IU for adults older than 70 years.8,26,27 However, recent research suggests that current AI recommendations for children and adults may be too low to maintain optimal levels (above 30 ng per mL) for calcium absorption and parathyroid hormone suppression.3,28 Based on these concerns, the American Academy of Pediatrics recently recommended doubling the minimum daily intake for children and adolescents to 400 IU

## **Hypothyroidism**

is a common endocrine disorder resulting from deficiency of thyroid hormone. In the United States and other areas of adequate iodine intake, autoimmune thyroid disease (Hashimoto disease) is the most common cause of hypothyroidism; worldwide, iodine deficiency remains the foremost cause.(11)

## **Causes of Hypothyroidism**

The most common cause of hypothyroidism is Hashimoto's thyroiditis. "Thyroiditis" is an inflammation of the thyroid gland(11)(12). Hashimoto's thyroiditis is an autoimmune disorder. With Hashimoto's, your body produces antibodies that attack and destroy the thyroid gland. Thyroiditis may also be caused by a viral infection.

## **Signs and symptoms of hypothyroidism**

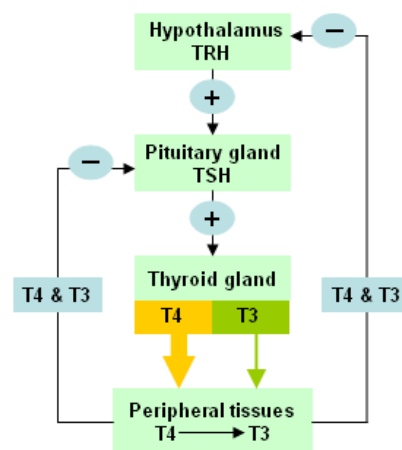
Hypothyroidism commonly manifests as a slowing in physical and mental activity but may be asymptomatic. Symptoms and signs are often subtle and neither sensitive nor specific.

### **The following are symptoms of hypothyroidism:**

- Fatigue, loss of energy, lethargy
- Weight gain
- Decreased appetite
- Cold intolerance
- Dry skin
- Hair loss



- Sleepiness
- Muscle pain, joint pain, weakness in the extremities
- Depression
- Emotional lability, mental impairment
- Forgetfulness, impaired memory, inability to concentrate
- Constipation
- Menstrual disturbances, impaired fertility
- Decreased perspiration
- Paresthesia and nerve entrapment syndromes
- Blurred vision
- Decreased hearing
- Fullness in the throat, hoarseness



### Hypothyroidism Risk Factors

Women, particularly older women, are more likely to develop hypothyroidism than men(11). You are also more likely to develop hypothyroidism if you have a close family member with an autoimmune disease(14). Other risk factors include:

- \* Race (being white or Asian)
- \* Age (growing older)
- \* Prematurely graying hair

- \* Autoimmune disorders such as type 1 diabetes, multiple sclerosis, rheumatoid arthritis, celiac disease, Addison's disease, pernicious anemia, or vitiligo
- \* Bipolar disorder
- \* Down syndrome
- \* Turner syndrome

### **Diagnosis of Hypothyroidism**\* Thyroid-stimulating hormone (TSH)

- \* T4 (thyroxine)

Lower-than-normal T4 levels usually mean you have hypothyroidism. However, some people may have increased TSH levels while having normal T4 levels. This is called subclinical (mild) hypothyroidism. It is believed to be an early stage of hypothyroidism.

If your test results or physical exam of the thyroid are abnormal, your doctor may order a thyroid ultrasound, or thyroid scan, to check for nodules or inflammation.(35)

### **Complications of hyperparathyroidism(13)**

are mainly related to the long-term effect of too little calcium in your bones and too much calcium in your bloodstream. Common complications include:

The loss of calcium often results in weak, brittle bones that fracture easily (osteoporosis).

Kidney stones Too much calcium in blood may lead to too much calcium in urine, which can cause small, hard deposits of calcium and other substances to form in kidneys. A kidney stone usually causes major pain as it passes through the urinary tract.

Cardiovascular disease Although the exact cause-and-effect link is unclear, high calcium levels are associated with cardiovascular conditions, such as high blood pressure and certain types of heart disease.

Neonatal hypoparathyroidism Severe, untreated hyperparathyroidism in pregnant women may cause dangerously low levels of calcium in newborns.

### **Effect of Vitamin D Supplementation on Thyroid Autoimmunity among Subjects of Autoimmune Thyroid Disease(13)(14)**

Hashimoto's thyroiditis (HT)(31) is a variant of autoimmune thyroid disorders (AITD) which has been associated with vitamin D (vit-D) deficiency. However, whether vit-D supplementation is linked to reduction of thyroid autoantibodies and improvement of thyroid function is not well characterized. The present study was planned to evaluate the effect of vit-D supplementation on possible improvement of thyroid autoantibody titer and thyroid hormone profile in patients with AITD subjects.(16)(35)

Vitamin-D levels were low in AITD patients in eastern India and, its supplementation in HT patients increased thyroid antibody titer and there was significant reduction in serum TSH and increased in free T4.

### **Autoimmune thyroid disease**

(AITD) is broadly classified into two types: Grave's disease and Hashimoto's thyroiditis (HT). HT is a polygenic in nature resulting from interplay between the genetic factor and environmental triggers, characterized by lymphocytic infiltration into the thyroid glands and thyroid specific autoantibodies.<sup>1</sup> HT is a typical T-cell-mediated autoimmune disease characterized clinically with diffuse

thyroid swelling with presence of thyroid autoantibodies (anti thyroid peroxidase [TPO] antibody with various form of thyroid dysfunctions.<sup>2</sup> Clinical manifestation is varied from overt hypothyroidism to subclinical hypothyroidism depending on the degree of immune-mediated destruction of thyroid follicular cell.<sup>(17)(18)</sup>

Vit-D has been demonstrated to have a role in thyroid disease. It is involved in modulating immune system, and it enhances the innate immune response while exerting the inhibitory action in adaptive immune system.<sup>2</sup> Nuclear vit-D receptor and the vitamin-D-activating enzyme  $1\alpha$ -hydroxylase (CYP27B1) is expressed in T-cell, B-cells, macrophage, and antigen-presenting cell (APC) such as dendritic cells (DCs), all are actively involved in immune response.<sup>3</sup> APC expresses major histocompatibility complex II antigen and costimulatory molecule, which is inhibited by vit-D; it not only prevents the maturation and differentiation of DCs but also halts their activation and survival, leading to decreased antigen presentation and T-cell activation. <sup>(19)</sup>Vit-D modulates the DCs expression of cytokine by inhibiting the production of interleukins 12, 13 and enhancing the production of interleukin-10. Therefore, it shifts Th1, Th17 T-cell moiety to Th2 subtype. There is evidence that it also modulates the antibody production from B-cell. <sup>(26)</sup>By and large, vit-D has the ability to suppress the adaptive immune reaction and enhance the innate immune action, which has favorable outcomes for various autoimmune disorder.

Efficacy of vit-D supplementation in vit-D deficient AITD<sup>(16)</sup> is controversial. Vit-D supplementation has shown decrease in thyroid autoantibody titers as reported by some investigators while has no effect by others.<sup>6</sup> The present study was planned to investigate the impact and magnitude of vit-D supplementation on thyroid function in subjects with HT.

The study was aimed to evaluate the effect of vit-D supplementation to the HT patients with Vit-D deficiency with subclinical hypothyroidism.(20)(21)

The objective was to study the effect of vit-D supplementation on thyroid autoantibody (anti-TPO antibody) titer and thyroid hormone profile (thyroid-stimulating hormone [TSH] and free T4) in patients with HT with subclinical hypothyroid state.

Vit-D deficiency is significantly common in HT patients in Eastern India and its supplementation in these patients did not show any beneficial effect on thyroid autoimmunity as evidenced by a significant increase in circulating anti-TPO antibody titers though there is significant reduction in the TSH levels.(22)

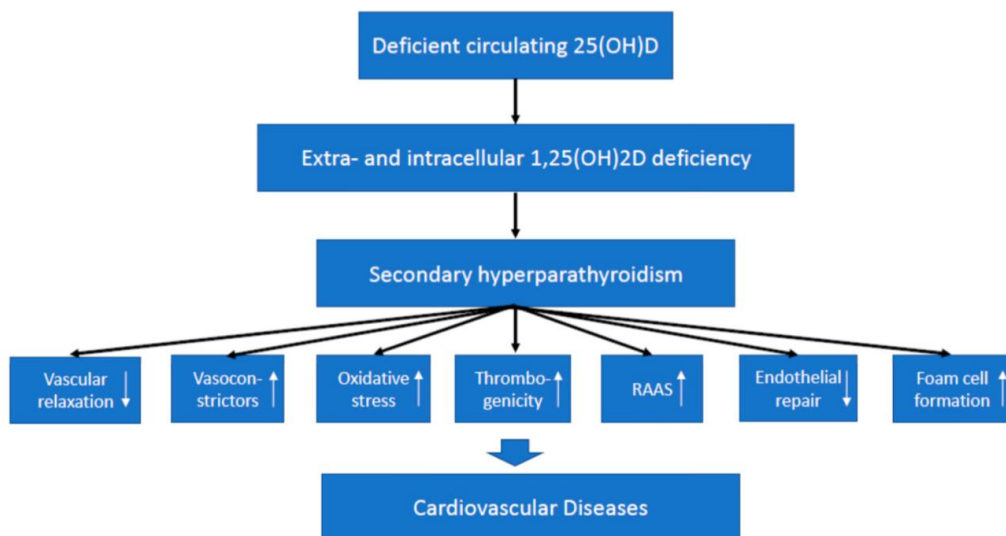
Hypothyroidism is believed to be associated with dyslipidemia and is considered a risk factor for the development of atherosclerotic cardiovascular diseases (ASCVD). Vitamin D, due to its steroid hormone action, retains cell function and controls the metabolism of lipids. Therefore, the present study was carried out to show the association of the risk factors of ASCVD and deficiency of thyroid hormones and vitamin D levels. (21)

## **Vitamin D Effects on The Cardiovascular System**

In general, vitamin D effects on cardiovascular health may be mediated either by effects on classic and emerging cardiovascular risk factors or by direct effects on the cardiovascular system [14,24,25].

In brief, both the VDR and the  $1\alpha$ -hydroxylase are present in vascular tissues such as endothelial cells and vascular smooth muscle cells (VSMCs), and also in cardiomyocytes [26]. In the vascular wall,  $1,25(\text{OH})_2\text{D}$  has several beneficial genomic effects, including a reduction in thrombogenicity, a decrease in vasoconstrictors, an inhibition of oxidative stress and atherogenesis, an improvement of endothelial repair, a reduction in foam cell formation, and vascular relaxation and dilatation. However,  $1,25(\text{OH})_2\text{D}$  can also induce the trans-differentiation of VSMCs into osteoblast-like cells, which may lead to vascular calcification [25,26].

In cardiomyocytes,  $1,25(\text{OH})_2\text{D}$  can induce several genomic and non-genomic effects, which regulate intracellular calcium metabolism [27]. There is evidence that, similar to the regulation of circulating  $1,25(\text{OH})_2\text{D}$ , the synthesis of  $1,25(\text{OH})_2\text{D}$  in the heart and the vasculature is regulated by PTH and FGF-23 [28,29]. In cardiomyocytes, FGF-23 results in hypertrophic growth [30]. Although vitamin D signaling in cardiomyocytes and the vascular wall is not completely clarified in detail, the available data indicate that  $1,25(\text{OH})_2\text{D}$  plays a pivotal role for adequate cardiac and vascular function. Various effects of vitamin D on the cardiovascular system may, in addition to VDR activation, also be mediated by PTH.



### Cardiovascular Disease in Severe Vitamin D Deficiency

A number of case reports have been published associating nutritional rickets with heart failure, but not with other forms of CVD such as hypertension, stroke, or myocardial infarction. In all these cases, young patients also suffered from secondary hyperparathyroidism and hypocalcemia. The cardiac effects were effectively cured by vitamin D and calcium administration [39,40]. However, heart failure or other forms of CVD have not been described in genetic forms of rickets such as vitamin D-dependent rickets type I and II. They are based on a lack of the 1-alpha hydroxylase enzyme or a deletion of the VDR, respectively. Both genetic disorders can be caused by more than 60 different mutations [41]. Their clinical symptoms usually present in infancy or early childhood and are similar to the phenotype of nutritional vitamin D-deficient rickets, including secondary hyperparathyroidism and hypocalcemia. Probably, CVD has not been described in these disorders because they are both rare pediatric diseases with relatively few known cases.

Hypocalcemia with heart failure has indeed been reported in a 41-year-old female patient with nutritional osteomalacia. Her cardiac failure improved promptly on correcting the hypocalcemia by vitamin D and calcium. Again,

however, CVD has not been reported in cases with other forms of osteomalacia such as tumor-induced osteomalacia. This is a rare endocrine disorder of disturbed vitamin D metabolism, predominantly in middle-aged adults. It is characterized by hypophosphatemia, phosphaturia, and inappropriately low serum levels of 1,25(OH)<sub>2</sub>D.

The biochemical changes are related to elevated FGF-23 concentrations(15)(20) Altogether, some toddlers or younger adults with rickets or osteomalacia may develop hypocalcemia-associated heart failure, but obviously not other forms of CVD. Conversely, significantly lower circulating vitamin D metabolites and plasma calcium concentrations have been reported in patients with advanced heart failure compared with healthy controls, with the lowest circulating 1,25(OH)<sub>2</sub>D concentrations and plasma calcium concentrations in the hypocalcemia range (<2.1 mmol/L) in those patients with early-onset of the disease

### **Cardiovascular Disease According to Genetic Analyses of Vitamin D Metabolism**

Genetic studies have the advantage that they are unaffected by lifestyle factors. With respect to vitamin D and CVD, genetic studies can be divided into two groups. Mendelian randomization is an analytical method that uses genetic variants as instrumental variables for modifiable risk factors such as circulating 25(OH)D that potentially affect CVD risk. Another group of genetic studies are association studies that analyze gene variants of non-modifiable risk factors such as VDR polymorphisms, which may affect CVD risk by influencing vitamin D signaling pathways.(16)(20)



## **Discussion**

Vitamin D is known for its primary role in bone and mineral homeostasis, and it has been shown recently that its deficiency is associated with various diseases such as cardiovascular disease, cancer, infection, and adiposity as well as osteoporosis. Interestingly, it has been shown recently that vitamin D has potent immunomodulatory effects and plays important roles in the pathogenesis of autoimmune diseases. Serum concentration of 25(OH)D is the best indicator of vitamin D status. It reflects vitamin D produced cutaneously and that obtained from food and supplements and has a fairly long circulating half-life of 15 days. In contrast to 25(OH)D, circulating 1,25(OH)<sub>2</sub>D is generally not a good indicator of vitamin D status because it has a short half-life of 15 hours and serum concentrations are closely regulated by parathyroid hormone, calcium, and phosphate. Levels of 1, 25(OH)<sub>2</sub>D do not typically decrease until vitamin D deficiency is severe. Therefore, in the present study we measured serum 25(OH)D rather than 1,25(OH)<sub>2</sub>D to ensure we are getting more accurate results. Few studies have been conducted in order to find any significant association between the levels of vitamin D and hypothyroidism and to determine whether vitamin D deficiency involves in the pathogenesis of hypothyroidism or rather a consequence of the disease and those that yielded conflicting results.

## **Conclusions**

In summary, the available data do not support a major effect of vitamin D supplement use in the general population or vitamin D (metabolite) administration in the clinical setting to reduce CVD risk. However, more research is necessary to assess whether personalized preventive and therapeutic strategies are effective in some subgroups, i.e., individuals with a combination

of low vitamin D status with specific gene variants and/or certain nutrition and lifestyle factors or those with severe vitamin D deficiency.

## **Summary**

In this review we summarize recent opinions on the possible role of vitamin D in the risk of thyroid diseases development. It may be concluded from the available data that vitamin D deficiency, particularly levels below 12.5 ng/ml should be considered as an additional, but important risk factor for development of thyroid autoimmunity, both chronic autoimmune thyroiditis and Graves' disease. A higher risk of Graves' disease development is also associated with several polymorphisms in the gene encoding for vitamin D binding protein and for the specific receptor of active form of vitamin D – 1,25-(OH)<sub>2</sub>D<sub>3</sub> in the respective target cells. Important for development of thyroid cancer appeared polymorphisms of genes encoding for vitamin D receptors and of genes encoding for the participating hydroxylating enzymes in thyroid tissue, leading to a diminished local 1,25-(OH)<sub>2</sub>D<sub>3</sub> formation capacity with following alteration of antiproliferatory, antiapoptotic and prodifferentiating efficacy of the latter. Whether supplementation with high doses of vitamin D or its analogues possesses preventive or therapeutic effect is an object of intensive studies.

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