INTRODUCTION

Vitamin D deficiency has been recognized as a very frequent vitamin deficiency worldwide.\cite{1} Giving that the synthesis of vitamin D is initiated in the skin by UVB radiation, persons with lower than normal exposure to sunlight are at higher risk of vitamin D deficiency, which is supported by scientific evidences.\cite{2} Vitamin D sufficiency is defined as blood concentration of 25-hydroxyvitamin D [25(OH)D] of at least 30ng/mL, according to The Centers for Disease Control and Prevention\cite{3} (Table1). Recent reviews have demonstrated that the number of individuals with inadequate blood levels of vitamin D is constantly increasing. Sufficient levels of vitamin D were found in 60% individuals in the period 1988-1994 and in 30% of individuals during the period 2001-2004.\cite{4} Severe vitamin D deficiency is defined as 25(OH)D blood level <10ng/mL and it has increased from 2% to 6% during the same period.\cite{4}

Table 1. Mayo Medical Laboratories Reference Ranges for Total Serum 25-hydroxyvitamin D [25(OH)D]\textsuperscript{a}

\begin{tabular}{ll}
Severe deficiency\textsuperscript{b} & <10 ng/mL \\
Mild to moderate deficiency\textsuperscript{c} & 10-24 ng/mL \\
Optimal\textsuperscript{d} & 25-80 ng/mL \\
Possible toxicity & >80 ng/mL \\
\end{tabular}

\textsuperscript{a} SI conversion factor: To convert 25(OH)D values to nmol/L, multiply by 2.496.
\textsuperscript{b} Could be associated with osteomalacia or rickets.
\textsuperscript{c} May be associated with secondary hyperparathyroidism and/or osteoporosis.
\textsuperscript{d} Levels present in healthy populations.
During the past few decades, vitamin D deficiency has been strongly linked with a wide range of autoimmune disorders, such as rheumatic disorders, multiple sclerosis, type 1 diabetes mellitus, inflammatory bowel disease, etc.\[5-7\] Other than well-known role in bone metabolism, vitamin D receptors have been found in many cells which constitute the immune system, such as dendritic cells, T lymphocytes, and monocytes.\[7\] Furthermore, vitamin D receptor polymorphism has been identified in many autoimmune diseases.\[8-9\] This implies an important role of vitamin D in proper functioning of the immune system and clear evidences that its deficiency causes disturbances in immune response and can initiate autoimmune processes.

Systemic lupus erythematosus (SLE) is a common rheumatic disease with complex etiology and epidemiology, high variability of clinical manifestation, and often non-predictive progression and outcomes. Estimations of prevalence of SLE differ greatly in different studies due to different methods used and assessment in different population groups. Therefore, the global prevalence ranges from 20 to 70 per 100,000.\[10\] Recently, the linkage between low vitamin D levels and SLE has been identified.\[11-13\] There are controversial opinions about this linkage in terms of causality. Namely, as previously stated, vitamin D evidently has immunomodulatory activity, and its deficiency can contribute to the development of autoimmune disorders, such as SLE. On the other hand, SLE diminishes functions of multiple organs, including kidneys in which 1-hydroxylation of 25OH)D takes place.\[14\] Furthermore, photosensitivity is one of the most pronounced features of SLE, and the lack of sun exposure may lead to vitamin D deficiency in these patients.\[15\] There are also evidences that corticosteroids which are excessively used in the treatment of SLE may interfere with vitamin D metabolism.\[16\]

In this review, we assess current views on the relationship between vitamin D deficiency and SLE, with the stress on studies dealing with causality between these two clinical entities.

**Metabolism of Vitamin D**

The most active form of vitamin D is vitamin D$_3$ or 1,25-dihydroxycholecalciferol [1,25(OH)$_2$D$_3$]. This form is obtained from food and it is also synthesized in the body. The synthesis begins in the skin where the conversion of 7-dehydrocholesterol to vitamin D and
this reaction is initiated by UVB radiation. Studies have shown that the production of vitamin D in the skin is highly related to exposure to sunlight.\cite{17,18} The form of vitamin D produced in the skin is still inactive. As vitamin D is a hydrophobic molecule, it is transported through the bloodstream by vitamin D binding protein (DBP). The next reaction occurs in the liver, where vitamin D 25-hydroxylase from cytochrome P450 complex catalyzes conversion of vitamin D to 25(OH)D.\cite{19} The main enzyme involved in this process is CYP2R1, although the expression and activation of this enzyme are still under investigation.\cite{20} Patients with mutation of gene for CYP2P1 have insufficient levels of 25(OH)D and 1,25(OH)\textsubscript{2}D\textsubscript{3}.\cite{21} After being synthesized in the liver, 25(OH)D is released into the bloodstream bound to DBP and transported to the kidneys where the final reaction occurs. C-1 hydroxylation is performed in proximal renal tubule by the enzyme 25(OH)D 1α hydroxylase from cytochrom P450 family.\cite{22} This results in the most active form of vitamin D - 1,25(OH)\textsubscript{2}D\textsubscript{3} to which most of the effects of vitamin D are attributed. Inactivation of vitamin D is performed by the enzyme 24-hydroxylase, which turns 1,25(OH)\textsubscript{2}D\textsubscript{3} into 1,24,25(OH)\textsubscript{3}D\textsubscript{3}, which is further metabolized to calcitroic acid.

Metabolism of vitamin D is regulated by several different mechanisms, based predominantly on the principle of negative feedback. Increased level of parathyroid hormone (PTH) is a result of hypocalcaemia and it enhances the activity of 25(OH)D 1α hydroxylase.\cite{23} In turn, increased levels of 1,25(OH)\textsubscript{2}D\textsubscript{3} result in decreased activity of 25(OH)D 1α hydroxylase.\cite{24} Regulation is also present at the transcription and translation level of 24-hydroxylase gene.\cite{25} Another regulator of vitamin D metabolism includes fibroblast growth factor 23 (FGF23) which prevents reabsorption of phosphate in the proximal tubule which in turn decreases levels of vitamin D.\cite{26} FGF23 is synthesized in bones and it is in negative feedback with circulating levels of 1,25(OH)\textsubscript{2}D\textsubscript{3}. Other hormones, such as calcitonin, prolactin, and estrogen have also been found to participate in regulation of vitamin D levels.\cite{27}

**Role of vitamin D in immunomodulation**

It has been found that many cells included in innate and acquired immune response contain VDR, such as macrophages, neutrophils, and B and T lymphocytes.\cite{28} Activation of VDR in immune cells starts signaling cascade leading to immunomodulatory effects. Vitamin D has been shown to produce potent effect on stimulation of macrophages during bacterial infections through VDR and CYP27B receptors.\cite{29} Another discovery was that macrophages and monocytes are able to produce 1,25(OH)\textsubscript{2}D\textsubscript{3} locally in tissues affected by tumor and
This paracrine secretion of vitamin D suggests its immunomodulatory activity. Furthermore, 1,25(OH)$_2$D$_3$ induces production of prostaglandin E$_2$ in macrophages which is well known as an immunosuppressant agent. To summarize, vitamin D deficiency can severely affect maturation and signaling pathways in which macrophages are actively involved during immune response. Studies have shown that vitamin D supplementation eliminates these effects. Regarding the effects of vitamin D on B lymphocytes, it has been noticed that activation of 1,25(OH)$_2$D$_3$ by VDR upregulation has a suppressive effect on proliferation of B-cells. This implies that vitamin D modulates B-cell response and production of antibodies, but the opinions are still controversial. Activated T cells (both Th1 and Th2 subtypes) show great expression of VDR. Binding of VDR to 1,25(OH)$_2$D$_3$ activates the translation of phospholipase C-γ1 (PLC-γ1). PLC-γ1 is crucial for t-cellular signaling pathways and activation of naive T-cells. Vitamin D acts through VDR receptors by changing secretion of cytokines, thus inhibiting activation of effector T-cells while stimulating activation of regulatory T-cells.

**Vitamin D deficiency in patients with SLE**

As shown in the previous chapter, vitamin D interferes with almost all the mediators of immune response. Therefore, the relationship between vitamin D deficiency and autoimmune diseases is one of the most popular topics today. When it comes to SLE, many studies have confirmed high incidence of vitamin D deficiency among patients with SLE. In one of the studies, 90% of patients with active SLE and 85% of patients with inactive SLE were vitamin D deficient. The main risk factors responsible for vitamin D deficiency in SLE patients were claimed to be lack of exposure to sunlight, use of drugs, such as hydroxychloroquine (HCQ), anticonvulsants that speed-up elimination of 25(OH)D, and possibly the existence of antibodies specific to vitamin D which increase its clearance. It is worthy to point out that autoimmune diseases, including lupus are more common and have more pronounced clinical manifestations in women than in men. This is also true for SLE. In some countries, such as Saudi Arabia, vitamin D deficiency was recorded in 80% of healthy women, while men had significantly higher levels of vitamin D. Results from studies from different countries differ a lot and they are hard to compare, because some of them included only the patients with active SLE while others included all the patients with SLE. Prevalence of vitamin D deficiency is always higher in patients with active SLE than in patients with inactive disease because the active inflammatory process stimulates catabolism of vitamin D.
Recommendations for the effective vitamin D supplementation in patients with SLE are not strictly defined. In one study, daily supplementation of 800 IU of vitamin D led to 25(OH)D levels higher than 75 nmol/L in 67% of treated patients. The dose of 2000IU resulted in 83% patients with vitamin D levels higher than 75 nmol/mL, so this is the currently recommended daily dosage for patients with SLE.[39]

Causality between vitamin D deficiency and SLE

Even though current research mainly focuses on the effects of vitamin D deficiency on the development and worsening symptoms of SLE, there are still reasons for controversy when it comes to causality issue between these two clinical entities. As explained before, vitamin D undoubtedly plays an important role in modulating immune response and there is rationale for the statement that its deficiency can cause autoimmune diseases, including SLE. However, autoimmune processes occurring in the clinical course of SLE can affect multiple organs causing nephropathy and photosensitivity. Nephropathy can cause decreased production of active form of vitamin D, 1,25(OH)₂D₃, by decreased activity of 25(OH)D 1α hydroxylase in the proximal renal tubule.[14] Photosensitivity of SLE skin lesions requires avoidance of excess exposure to sunlight, which has as a consequence decreased conversion of 7-dehydrocholesterol into vitamin D in the skin, which is the reaction that requires exposure to UV radiation.[40] Another fact is that corticosteroids are the main treatment option in patients with SLE, and there are evidences that high dosages of corticosteroids used long-term can interfere with metabolism of vitamin D and cause its deficiency.[16]

CONCLUSION

Vitamin D deficiency is very common in patients with both active and inactive form of SLE. Both vitamin D deficiency and SLE are more common in females than in males. Vitamin D deficiency especially affects people who live in the areas with low number of sunny days during the year. Although further research is certainly needed, we can safely say that vitamin D supplementation is recommended in patients with SLE, regardless of the direction of causality between these two clinical entities.

REFERENCES

30. Abe E, Miyaura C, Tanaka H, Shiina Y, Kuribayashi T, Suda S, et al. 1 alpha,25-dihydroxyvitamin D3 promotes fusion of mouse alveolar macrophages both by a direct


