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Serum Vitamin D Levels in Children with Immune Thrombocytopenia: Review Article

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ABSTRACT

Background: Platelet disorders include immune thrombocytopenia (ITP). In ITP, the child's platelet count is too low, therefore blood does not clot normally. Small blood cells called platelets are produced in the bone marrow. Platelet degradation by antibodies and/or cells may have a role in ITP's pathophysiology, albeit this is not fully understood. Children who are newly diagnosed or chronic ITP type often have vitamin D (VD) deficiency. Since of this, immune cells that express VD nuclear receptor (VDR) are helpful because they can break down VD.

Objective: Assessment of correlations of vitamin D Level among children who have immune thrombocytopenia.

Methods: We scoured scholarly journals and information repositories including PubMed, Google Scholar, and Science Direct for studies on serum vitamin D levels and immune thrombocytopenia. Only the most recent or comprehensive study conducted between November 2001 and July 2020 was considered. The authors also analysed references from comparable works. As a result, non-English documents have been overlooked due to a lack of resources to translate them. Unpublished articles, oral presentations, conference abstracts, and dissertations were all generally agreed upon not to constitute legitimate scientific investigations.

Conclusion: Among newly diagnosed ITP cases, especially in children, cytokine abnormalities have been identified. Literature on VD and ITP, pathogenesis and medical diagnosis is poorly reviewed. The use of VD can also be helpful for new diagnosed as well as chronic ITP patients.

Keywords: Immune thrombocytopenia, Children, Vitamin D.

INTRODUCTION

The highest frequency of ITP is between the ages of 2 and 5, although the age varies from early childhood to older people. The disorder is self-limited in most children with resolution in 80% of patients within 6-12 months of diagnosis. A platelet-facing autoantibody develops in a tiny number of youngsters, about 1 in 20,000, 1–4 weeks following exposure to a specific viral infection **(1).**

Platelet degradation by antibodies and/or by cells may have a role in the pathophysiology of ITP, however this is still poorly understood. Recent research, however, has revealed the importance of the bone marrow niche, cytokine imbalances, and T-cell impairments. The most common cause of ITP is the binding of IgG autoantibodies to platelets and MKs. These antibodies target highly expressed surface antigens including glycoprotein (GP) IIb 3 (GPIIbIIIA) and GPIb- IX-V **(2)**.

When platelets containing bound autoantibodies are recognised by phagocytes expressing Fc-receptors, this leads to increased antibody-mediated platelet phagocytosis and, in particular, spleen injury. Furthermore, MK development and survival could be hampered or even prevented by autoantibody binding. Furthermore, the glycoprotein hormone thrombopoietin (TPO) produced in the liver cannot be used to treat decrease in platelet counts **(3)**.

A novel functional defect of TPO has been added to the pathogenesis of the disease, as nearly two-thirds of people with ITP have either normal or reduced levels of plasma TPO. Despite an increased quantity of MK in certain patients' bone marrow, there are several symptoms of morphological defects, including apoptotic ultrastructure and Caspase-3 activation, as well as platelet destruction. In addition to these cellular deficits, ITP patients also have an unbalanced cytokine profile, with decreased levels of cytokines like interleukin (IL)-2, interferon (IFN), and IL-17 in their blood **(4)**.

Within the first three months following diagnosis, clinical classification of ITP is possible into three stages, with the first stage being the time of initial diagnosis. Symptoms of intermittent thrombocytopenic purpura (ITP) typically last between three and twelve months, but those of chronic ITP persist for longer. Recently diagnosed acute ITP was once a term used only to describe adolescents. If immediate treatment is needed for bleeding symptoms, a diagnosis of ITP is considered life-threatening. The vast majority of adult patients will experience persistent symptoms over time **(5).**

Secosteroids, short for "separated steroids," are the many forms of vitamin D. As a result of differences in their side chains, vitamin D2 and vitamin D3 function differently. D2 has a methyl group at carbon 24 and a double bond between carbons 22 and 23 on its side chain. One of the numerous analogues of vitamin D is secosteroids, commonly referred to as split steroids. The structural and physiological characteristics of vitamins D2 and D3 differ from one another. As part of its side chain, the D2 molecule has a double bond between carbons 22 and 23 and a methyl group on carbon 24 **(6).**

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Sources of Vitamin D:

1- Ultraviolet irradiation of 7-dehydrocholesterol in the skin:

The dermis, which is rich in connective tissue, is the thicker of the skin's two primary layers, while the epidermis, which is thinner, is the outermost. Outermost and deepest layers of the epidermis are called the stratum corneum and the stratum lucidum, followed by the stratum granulosum and the stratum spinosum**.** The skin undergoes a photochemical reaction that transforms 7-dehydrocholesterol into vitamin D3. The highest levels of 7-dehydrocholesterol are found in the basal and spinosum strata of the epidermis. Thus, these two layers produce the most pre-vitamin D3, while the other layers produce far less **(7).**

When exposed to UVB rays (with a wavelength of 290-315 nanometers), the skin's 7-dehydrocholesterol cutaneous is converted to pre-vitamin D3, and then to vitamin D3 **(8)**.

Quantity (intensity) and quality (right wavelength) of UVB irradiation penetrating to the depth of 7-dehydrocholesterol in the basal and spinosum strata are the two most essential determinants of pre-vitamin D3 production **(7).**

2- Ingested vitamin D of animal or plant origin:

Vitamin D-containing foods are relatively rare in the wild. Foods such as salmon, tuna, and mackerel, along with various types of fish and fish liver oils, are highly recommended. Beef liver, cheese, and egg yolks all contain trace levels of vitamin D. Both vitamin D3 (cholecalciferol) and its metabolite 25(OH)D3 can be found in certain foods. Vitamin D2 levels in most mushrooms tend to be quite consistent (ergocalciferol) **(9).**

Metabolism of vitamin D

1) Synthesis

a) Photobiogenesis

7-dehydrocholesterol, often known as provitamin D3, is the first step in the body's synthesis of vitamin D. 7-dehydrocholesterol is the precursor to vitamin D3 when exposed to UVB rays between 280 and 320 nm **(10)**, Previtamin D3 is isomerized to vitamin D3 by subsequent thermal reaction in the body. Synthesis of vitamin D3 requires a precursor of 7-dehydrocholesterol and sunlight at pecefish wavelength and angle **(11).**

b) Hepatic activation

Because of its solubility in fat, vitamin D is metabolized in the small intestine. Incorporation into chylomicrons **(12),** Vitamin D is absorbed quickly through the skin and sent to the liver, where the hepatic hydroxylase enzyme converts it to 25(OH) (DBPs). The concentration of 25-hydroxyvitamin D in the blood is widely considered to be an excellent marker of vitamin D status **(12)**.

c) Renal activation

25 Hydroxy vitamin D is metabolized in kidney to produce the active form1, 25 dihydroxy vitamin D. This process is regulated by several factors including serum phosphorus, calcium and parathormone (PTH) **(13).**

2) Absorption of vitamin D

The involvement of fat in a meal with a supplement of vitamin D3 increases the absorption of the drug **(14)**.

3) Transport of vitamin D

Ninety percent of vitamin D pathway metabolites are transported by vitamin D-binding proteins (DBPs) and ten percent by albumin; the remaining one percent is found in a free circulating form **(15).**

4) Excretion of vitamin D

Vitamin D's primary excretory source is bile. Until secretion, vitamin D metabolites may be conjugated in the liver **(16).**

Biological action of vitamin D

Classic vitamin D action in intestine:

Vitamin D facilitates the synthesis in the small intestine of calcium and phosphorus.

Skeleton:

Bone mineralization and calcium and phosphate serum elevation are two of vitamin D's primary effects **(17).**

After being converted to 1,25(0h) 2D intracellularly, 25-hydroxyvitamin D enables an increase in bone density by enabling separation of osteoblasts and minerals **(18).**

Kidney: The effect of 1,25 (OH)D3 is its own hemostasis control **(16).**

Parathyroid glands

1.25 (OH) 2D decrease parathyroid hormone synthesis and secretion and inhibit the growth of parathyroid cells when vit D is low, PTH increases bone resorption to meet body calcium demand **(11)**.

Non classical action of vita min D: Function Regulation of immune

Possible roles for vitamin D and 1,25(OH)2D vitamin D receptors (VDRS) interact with active human inflammatory cells to regulate the immune response **(19).**

Vitamin D appears to alter immune function in two ways, either upregulating the innate immune system or lowering adaptive immune regulation, as evidenced by the ability of macrophage at activated illnesses to generate 1,25 (OH)2D and 1.25-Hydroxyvitamin D's capacity to inhibit T-cell proliferation **(20).**

Vitamin D concentrations in the blood of Kids with immune thrombocytopenia

Children with newly diagnosed or chronic ITP type often have vitamin D (VD) deficiency. Therefore, there are immune cells capable of VD metabolism that express VD nuclear receptor (VDR) [21]. T-cell cytokine generation, lymphocyte activation and proliferation, promyelocyte-to-monocyte differentiation, and other hematopoietic processes are all regulated by VD [22].

Multiple investigations have shown that VD can suppress IFN- π and IL-2 production in human PBL and T cell lines (IL-2). These hormones suppress T cell inflammation by increasing synthesis of interleukin 4 (IL-4). In patients with ITP, age is favourably connected with serum IFN- π levels, CD4+ lymphocyte counts, and the total number of killer cells [23].

Cytokine abnormalities have been detected in newly diagnosed individuals with ITP, notably in youngsters. New cases of ITP in both children and adults were associated with elevated levels of IL-4 in the blood. Cytokine abnormalities, namely variations in IL- 2, IL-3, and TNFα, may contribute to the aetiology of chronically diagnosed ITP in children, as seen by significant disparities in cytokine levels between paediatric patients and healthy controls. A high level of TNF--α is associated with a higher risk of bias in the identification of ITP in otherwise healthy youngsters [23].

Inadequate VD levels are between 50 and 75 moll/L, whereas levels below 50 moll/L indicate a deficiency [24].

The immune cells that are affected by VD's immunomodulatory attacks are numerous. These cells include monocytes, macrophages, dendritic cells (DCs), T lymphocytes, and B lymphocytes. The likelihood of contracting an autoimmune disease is thought to be decreased by VD as well. Several immunological illnesses have also been linked to VD [24].

VDRs are essential for T cell-mediated immunity and is widely expressed in both T cells and macrophages. In addition, numerous autoimmune and immune-mediated disease patients had significantly lower serum VD levels compared to the general population [24].

Literature on VD and ITP, pathogenesis and medical diagnosis is poorly reviewed. Several examined levels of 25-hydroxylate vitamin D3 in peripheral blood [1,25(OH)2D3] and 1,25-dihydroxyvitamin D3. Patients with ITP had significantly lower peripheral blood levels compared to healthy controls, according to the results of the study. The most common link between VD insufficiency and ITP does not seem to have a clear pathophysiological mechanism of immunomodulatory effects [25].

VD may modulate the immune system by inhibiting IFN- π production, for example. Vitamin D3 derivatives have a role in immunomodulation, and recent research into their effect on the suppression of the IFN- π gene supports this role [25]. When elevated levels of IFN-. Play a significant role in the aetiology of diseases, such as in the case of multiple sclerosis, VD is used as a novel pharmaceutical technique. Those who have just been diagnosed with ITP, as well as those who have had the condition for some time, may benefit from VD treatment [25].

The genes responsible for making tumour necrosis factor alpha are among those shown to be downregulated by VD, according to multiple research projects. Serum TNF- levels were shown to be lower in people who had higher vitamin D levels. In a healthy population, the prevalence of VD is inversely related to that of TNF-alpha, and there is some evidence that VD protects against inflammatory diseases like cardiovascular disease and rheumatoid arthritis. To clarify the connection between VD and TNF alpha, however, more research is required. Alternative to anti-TNF-alpha medication for the treatment of autoimmune diseases like ITP is vitamin D therapy [26].

Hypovitaminosis D can cause immunological irregularities in the development of chronic ITP, while VD treatment can reduce the risk of chronic illness by changing the immune system [27].

Children with ITP, whether newly diagnosed or chronic, frequently exhibit VD deficiency. Therefore, ITP patients have an advantage beyond VD [26]. **Petrovic *et al.*** [28] showed that children with ITP, like those with other autoimmune disorders, frequently suffer from Hypovitaminosis D. Hypovitaminosis D at the time of diagnosis exacerbates the severity of ITP in children, suggesting that therapy with VD could be a novel strategy to treat this ailment. **Hesham *et al.*** [29] found that children with chronic immunological thrombocytopenic purpura have been found to have a strong correlation with a variation in vitamin D receptor gene (Cdx2). Low serum vitamin D levels were also linked to chronic inflammatory thrombocytopenic purpura in children.

CONCLUSION

Among newly diagnosed ITP cases, especially in children, cytokine abnormalities have been identified. Literature on VD and ITP, pathogenesis and medical diagnosis is poorly reviewed. The use of VD can also be helpful for newly diagnosed and chronic ITP patients.

RECOMMENDATIONS

Children with chronic ITP benefit greatly from vitamin D therapy. Early detection, disease control, and the implementation of effective therapy options can only be achieved through widespread genetic screening for polymorphism in ITP.

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