

# Relation of Vitamin D and Immunity with Reference to Unani System of Medicine- A Review

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**Abstract:-** Vitamin D deficiency is associated with an increased risk of many adverse health effects. Vitamin D plays an important role in immunity and its classic effects on calcium and bone homeostasis. Enzymes that metabolize vitamin D and vitamin D receptor (VDR) are present in many cell types, including various immune cells such as antigen presenting cells, T cells, B cells, and monocytes. Vitamin D has the ability to play an autocrine role in the local immune environment. Vitamin D can regulate innate and adaptive immune responses. Vitamin D deficiency is related to decreased autoimmunity and increased susceptibility to infection. The beneficial effects of vitamin D supplementation on individuals lacking autoimmune diseases may exceed its effects on calcium and bone homeostasis. The main concern of the Unani medical system is human health, and its maintenance is the main function of *Tabiat* (immunity). *Tabiat* plays role in different stages of disease. If it exceeds time, the disease process will develop. Unani physician offers a variety of natural therapies, and regiminal therapy is one of them. The main purpose of this review article is to explore this ancient holistic pathy and establish a connection with modern theory.

**Keywords:-** VDR, *Tabiat*, Autocrine, Regiminal.

## I. INTRODUCTION

Vitamin D<sub>3</sub> is considered to be a micronutrient necessary for calcium homeostasis and bone formation<sup>1,2</sup>. However, vitamin D<sub>3</sub> is also an endogenous hormone when the skin is exposed to sufficient amounts of UV-B<sup>3</sup>. The form of vitamin D deficiency can cause severe bone mineralization defects and pronounced hypocalcemia<sup>4</sup>, and it usually affects patients with serum vitamin D levels below 20 nmol/L (8 ng/ml). In the United States and other countries, the historical strategy of supplementing infants with at least 200 IU (5 µg) of vitamin D per day has successfully reduced the incidence of rickets disease; however, today, the disease is not uncommon<sup>5-8</sup>. The first evolutionary function of VDR is to control metabolism to strongly support the evolution of the immune system of ancestral vertebrates<sup>9</sup>. Therefore, VDR and its ligands are the first specialised structure to resist bacterial and viral infections and multiple sclerosis<sup>10-11</sup>. As well as regulating innate and adaptive immunity, such as preventing autoimmune diseases such as rheumatoid arthritis. Before

taking on the extra task of regulating bone metabolism<sup>12-13</sup>. Therefore, vitamin D deficiency can lead to an increase in bone diseases such as rickets<sup>14</sup>, and may also be one of the reasons for the increase in vulnerability to viral infections (such as coronavirus COVID -19 outbreak), especially in the elderly<sup>15</sup>.

## II. SOURCE AND METABOLISM OF VITAMIN D

Vitamin D can come from three potential sources: food sources, endogenous UVB-dependent products and supplements. In humans, vitamin D is mainly synthesized in the skin after exposure to UVB rays, and only a small part comes from food. Rarely unenriched natural products, such as oily fish (salmon, mackerel, sardines, cod liver oil) or certain types of mushrooms (shiitake), especially if they are sun-dried, the two main forms in corresponding amounts One, cholecalciferol (vitamin D<sub>3</sub>) or ergocalciferol (Vitamin D<sub>2</sub>)<sup>16-18</sup>. Since vitamin D is produced by the skin after exposure to ultraviolet B rays, its synthesis is affected by latitude, season, sunscreen use, and skin pigmentation. Melanin absorbs UVB rays by inhibiting vitamin D synthesis from 7-dihydrocholesterol. The first vitamin D compound is inactive and then hydroxylated in the liver to form 25 OH vitamin D<sub>3</sub> (25 D). 25 D is also an inactive compound, but it is the most reliable way to measure your vitamin D status. In the kidney, 1- $\alpha$ -hydroxylase (CYP27B1) converts the active compound 1,25 dihydroxy vitamin D (1,25 D) or calcidiol, an enzyme stimulated by parathyroid hormone. The 1.25 D level is tightly regulated in the negative feedback loop. 1.25 D acts in the gut to stimulate the reabsorption of calcium; It acts on bones to promote differentiation and calcification of bone osteoblasts. Active hormones act on these tissues by binding to vitamin D receptors (VDR). The complex dimerizes with the retinoid X receptor (RXR)<sup>19</sup>.

## III. VITAMIN D AND IMMUNITY

The first evidence that vitamin D may be an important enhancer of innate immunity comes from the use of cod liver oil in tuberculosis treatment<sup>20</sup>. Many tissues other than bone and gut, including cells from bone marrow, brain, colon, breast and malignant cells, vitamin D expresses VDR. And immune cells suggest that vitamin D may have functions other than calcium and bone homeostasis<sup>21</sup>. In addition, tissues other than kidney express 1- $\alpha$ -hydroxylase and can convert 25D to 1.25D in non-renal

compartments<sup>16,22,23</sup>. Therefore, in addition to endocrine function, vitamin D can act in a paracrine or autocrine manner. Some of the more recently recognized unusual effects of vitamin D include effects on cell proliferation and differentiation, and immunological effects that maintain tolerance and promote protective immunity. Vitamin D can act in a paracrine or autocrine manner in an immune environment, as antigen presenting cells (macrophages and dendritic cells [DC]), T cells, and B cells have a mechanism to synthesize and respond to 1.25 D.

The extrarenal enzyme 1- $\alpha$ -hydroxylase in macrophages differs from renal hydroxylase in that it is not regulated by PTH<sup>24</sup>. Instead, it depends on the circulating 25 D level or can be induced by cytokines such as interferon (IFN) F, interleukin (IL) 1, or tumor necrosis factor (TNF $\alpha$ )<sup>25</sup>.

There are some cross-sectional studies linking low vitamin D levels to increased infections. One report studied about 19,000 subjects between 1988 and 1994. People with low vitamin D (G30 ng / mL) levels are more likely to report upper respiratory infections recently than those with high vitamin D levels. Adjust for variables such as season, age, gender, weight, and race<sup>26</sup>. A well-designed double-blind placebo study using objective result, nasopharyngeal swab culture (not self-reported) and therapeutic doses of vitamin D showed that the incidence of influenza infection caused by taking vitamin D was statistically significant Reduction (42%)<sup>27</sup>.

The positive effect of vitamin D on protective immunity is partly due to its effect on the innate immune system. It is known that macrophages are able to recognize lipopolysaccharide (LPS) through the toll-like receptor (TLR), which replaces bacterial infection. The involvement of TLR leads to a series of events that produce peptides with strong bactericidal activity, such as Cathelicidin and  $\beta$ -defensin<sup>428</sup>. These peptides localize together with damaged bacteria in the phagosome, thereby destroying the bacterial cell membrane and they have effective antibacterial activity<sup>29</sup>. Vitamin D plays an important role in the innate antibacterial response. Binding of the TLR causes an increase in the expression of 1- $\alpha$ -hydroxylase and VDR<sup>29-30</sup>. This causes the 1,25 D-VDR-RXR heterodimers to bind to the vitamin D response elements of the Cathelicidin and beta-defensin 4 genes and then transcribe these proteins. Cathelicidin transcription is strictly 25D dependent<sup>29</sup>. In addition to enhancing chemotaxis and phagocytosis of innate immune cells<sup>31</sup>, calcitriol, VDR, and retinoid X receptor complex also directly activates antimicrobial peptides such as  $\beta$ 2 defensin (DEFB), and cathelicidin Microbial peptide transcription (hCAP18)<sup>32-34</sup>.

Early studies on the effect of vitamin D on human adaptive immune cells showed that enzymes that activate nuclear VDR and vitamin D are expressed in T cells and B cells<sup>35</sup>. In particular, the VDR of these cells is very low at rest, however, after activation and proliferation, T cells and B cells significantly regulate the expression of VDR and allow up to 500 vitamin D-sensitive genes to affect the

differentiation and proliferation of these cells<sup>36-38</sup>. Recent studies have confirmed that calcitriol has other direct effects on B cell homeostasis, including inhibiting memory and plasma cell formation and promoting apoptosis of B cells that produce immunoglobulin. Control of B cell activation and proliferation may be of important clinical significance in autoimmune diseases because B cells producing autoreactive antibodies play an important role in the pathophysiology of autoimmunity<sup>39-41</sup>. Calcitriol can inhibit proliferation and differentiation of T helper cells and also regulates helper T cells (Th) and cytokines<sup>42</sup>. In particular, treatment of T cells with calcitriol or analogs inhibits the pro-inflammatory cytokines Th1 (IL2, interferon-, tumor necrosis factor  $\alpha$ ), Th9 (IL9) and Th22 (IL22),<sup>43-48</sup>. The secretion of cytokines further inhibits the production of inflammatory Th2 cytokines (IL3, IL4, IL5, IL10)<sup>49</sup>. Th17 cells that produce IL17 are also affected by vitamin D. Inhibition of Th17 activity plays an important role in the treatment of autoimmune diseases such as obese diabetic mice (NOD)<sup>50</sup>. Recently, calcitriol directly inhibits IL17 production at transcriptional level<sup>51</sup> and activated human T-cells exposed to calcitriol produced significantly decreased levels of IL17, interferon- $\gamma$  and IL21.<sup>52</sup>

#### IV. UNANI CONCEPT OF IMMUNITY

According to the concept of Unani Medical, nature has given the power to protect health. It provides thousands of systems and control mechanisms for each cell, tissue and the entire body. Some of these functions work within cells, some functions work between cells, and other functions work throughout the body to maintain health<sup>53</sup>. The famous Unani scholar Ali Bin RabbanTabri wrote in his book FirdousalHikmat: "Tabiat is considered the governing power of the body and Tabiat performs the governing function of the body with the help of many physical forces called QuwawateTabaiyya. Physical Faculty), QuwateHaiwania (Vital Faculty) and QuwateNafsania (Nervous Faculty)". Therefore, the main function of Tabiyat is to provide general management and defense or immunity against organisms<sup>54</sup>.

Tabiat is defined as a collection of human structure, function and psychological characteristics. Hippocrates believed that everyone has a special ability called the body's defense mechanism, or expressed in the language of Unani Tabiat Muddabare Badan. This Tabiat is the best doctor and maintains the balance of four humours of the body. To maintain health, the quantity and body fluids must be adjusted according to the quality of the body's natural chemical components<sup>55</sup>.

Tabiat or the effectiveness of Quwwat-e-Muddabira Baden is due to diet, physical, psychological stress, hormones, etc. It will be affected by many exogenous and endogenous factors. Tabiyat-e-Insaniah controls all biochemical processes and physiological functions of the human body and also protects Aetidal Mizaj<sup>56</sup>.

Unani Medicine believes that diet and regimes can improve health, prevent and cure diseases. In this holistic medical system, the best way to improve health is to

strengthen tabiat (immunity) through immunomodulators, maintain a balanced temperament, maintain a humorous balance of quality and quantity, and the AsbabeSittaZarooriya (six of life essential elements) and adoption of maddiwa gair madditadabeer (i.e. regimenal therapy and counselling) MunzijwaMushil (concoctive and purgative) therapy and Ilajbilghiza (Dieto-therapy)<sup>57</sup>.

Zakaria Razi said in "Kitabul Murshid" that "Tabiat relieves diseases and expels waste materials from human body and living beings." The existence of Tabiat can be understood through examples such as the healing of small wounds without any treatment and the improvement or cure of various pains and diseases after deep sleep or over time. All this comes from the administrative and managing power of Tabiat. Life-related functions such as regeneration, growth and development are found only in living bodies. Corpses do not accept any renewal and do not act with any medicine, because there is no Tabiat in corpses<sup>58</sup>.

Regimenal therapy (Ilaj-bil-tadbeer) is one of the most popular treatment methods and has been practiced by ancient Unani scholars since ancient times. Basically, the application of certain special technologies or physical methods improves the structure of the human body by eliminating waste and improving the body's defense mechanism. Fasd (blood draw / puncture), Ta'aleeq (hirudotherapy) and Hijaamat (cupping) are important parts of the treatment. Ibn-e- Sina, an eminent Unani scholar wrote in his famous book "Canon of Medicine", that there are almost 36 regimens, amongs them "hammam" is one of the beneficiary regimes for increasing immunity.

The "Hammam" (Turkish bath), also known as the healing bath, is one of the oldest Unani therapies used in the treatment of some diseases. The bathhouse is held in a place reserved for the bath. The bathroom consists of several rooms, each opening into an adjacent room / another room, with special arrangements and conditions personalized according to the disease to be treated. Apart from all the benefits of Hammam one among them is that it strengthens body immunity against certain diseases<sup>59</sup>. Like Riyazat and Dalq, Hammam is a part of the Asbab-e- GhairZaroriya, which means that they are not essential to life's existence but will be healthy if done. Stay healthy under the conditions and regain your health or illness when the body is sick. The overall combination of Turkish bath with diet and exercise measures can activate the immune system and improve overall health.

#### ➤ *Hammam Shamshi (Sunbathing)*

In this case, the body will be exposed to direct sunlight.

#### ➤ *Benefits And Use*

Sunlight is a source of vitamin D3. Vitamin D3 can strengthen bones by aiding in calcium absorption. It is generally recommended to spend 15-30 minutes in the morning under direct sunlight<sup>60</sup>.

## V. CONCLUSION

In recent years, research has confirmed a strong association between vitamin D and body immunity (innate and adaptive). In very large-scale tissue, a body cell, including an immune cell, expresses nuclear VDR and has an enzyme that metabolizes vitamin D for the local, autocrine and paracrine conversion of provitamin D 25 D to the active form of vitamin D, i.e. calcitriol or D3. This process is critical for immune function. Therefore, impaired or insufficient vitamin D levels can reduce the body's immune function. This suggests that vitamin D supplementation can alter the course of autoimmune diseases. It is not clear at what serum level vitamin D supplementation can begin. Also, what dosage form (D2 or D3 form) of vitamin D will be effective? This will require larger clinical studies in the future.

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