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Review paper

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

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ABSTRACT

Inadequate levels of Vitamin D are linked to an elevated risk of numerous adverse health outcomes. This vitamin holds a crucial role in immunity and is traditionally recognized for its impact on calcium regulation and bone stability. Various cell types, including immune cells like antigen-presenting cells, T cells, B cells, and monocytes, harbor enzymes responsible for metabolizing vitamin D and vitamin D receptors (VDR). Vitamin D exhibits an autocrine role within the local immune environment, influencing both innate and adaptive immune responses. A deficiency in vitamin D is associated with reduced autoimmunity and heightened susceptibility to infections. Interestingly, the positive effects of vitamin D supplementation extend beyond its influence on calcium and bone stability, particularly in individuals without autoimmune diseases. In the Unani medical system, which prioritizes human health, the primary function of Tabiat (immunity) is to maintain well-being. Tabiat plays a critical role in various disease stages, and if not properly managed, it can contribute to the progression of the disease. Unani physicians employ diverse natural therapies, with regiminal therapy being one of them. This review article aims to delve into this ancient holistic approach and establish connections with modern theories, emphasizing the Unani system's focus on promoting overall health and preventing disease through immune system management.

1. Introduction

Vitamin D3 serves as a micronutrient essential for maintaining calcium balance and promoting bone formation. Beyond its role in nutrition, vitamin D3 transforms into an endogenous hormone upon exposure of the skin to adequate UV-B radiation (Holick, 2018). Deficiency in this vitamin can result in severe bone mineralization issues and significant hypocalcemia, typically observed in individuals with serum vitamin D levels below 20 nmol/L (8 ng/ml) (Vintilescu et al., 2019; Lu et al., 2019). Historically, supplementing infants with a daily dose of at least 200 IU (5 µg) of vitamin D proved effective in reducing the incidence of rickets in the United States and other nations. However, despite these efforts, the prevalence of the disease persists today. The primary evolutionary function of the vitamin D receptor (VDR) is to regulate metabolism, playing a pivotal role in supporting the immune system's evolution in ancestral vertebrates. VDR and its ligands serve as the earliest specialized defense against bacterial, viral inf-

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-ections, and autoimmune diseases like rheumatoid arthritis by influencing both innate and adaptive immunity.

2. Source and Metabolism of Vitamin D

Vitamin D can be acquired from three primary reservoirs: dietary sources, endogenous production dependent on UVB exposure, and supplements. In humans, vitamin D synthesis predominantly occurs in the skin following exposure to UVB rays, with a minority derived from food. Natural, unfortified sources such as oily fish (salmon, mackerel, sardines, cod liver oil), and specific mushrooms (shiitake), particularly when sun-dried, provide two main forms in equivalent proportions – cholecalciferol (vitamin D3) or ergocalciferol (Vitamin D2) (Özkan, 2010). Given that vitamin D is synthesized in the skin through exposure to ultraviolet B rays, factors such as latitude, season, sunscreen application, and skin pigmentation influence this process (Van de Peppel & van Leeuwen, 2014). Melanin, by absorbing UVB rays, hinders the synthesis of vitamin D from 7-dihydrocholesterol. The initial vitamin D compound remains inactive until it undergoes hepatic hydroxylation to form 25 OH vitamin D3 (25 D). While 25 D is also inactive, it serves as the most reliable indicator of vitamin D status. Subsequently, in the kidneys, 1-α-hydroxylase (CYP27B1) catalyzes the conversion of 25 D into the active compound dihydroxy vitamin D (1,25 D) or calcidiol, under the stimulation of parathyroid hormone. This active form, 1.25 D, is meticulously regulated in a negative feedback loop, acting on the gut to enhance calcium reabsorption and on bones to facilitate the differentiation and calcification of bone osteoblasts. The active hormone exerts its effects on these tissues by binding to vitamin D receptors (VDR), forming a complex dimer with the retinoid X receptor (RXR).

3. Vitamin D and Immunity

The initial inclination towards vitamin D as a crucial enhancer of innate immunity traces back to the historical use of cod liver oil in tuberculosis treatment. Besides its conventional roles in bone and gut health, vitamin D receptors (VDR) find expression in diverse tissues, including bone marrow, brain, colon, breast, and malignant cells, suggesting functions beyond calcium and bone homeostasis (Mughal, 2011). Furthermore, tissues outside the kidneys express 1-α-hydroxylase and can convert 25D to 1.25D in non-renal compartments. Thus, in addition to its endocrine role, vitamin D can act in a paracrine or autocrine manner. The extrarenal enzyme 1-α-hydroxylase in macrophages, unlike renal hydroxylase, is not regulated by PTH24 but depends on circulating 25 D levels or can be induced by cytokines such as interferon (IFN), interleukin (IL), or tumor necrosis factor (TNFα) (Chun et al., 2014; Vintilescu et al., 2019). Several cross-sectional studies establish a connection between low vitamin D levels and heightened susceptibility to infections. One study spanning 1988 to 1994 involving approximately 19,000 subjects revealed that those with low vitamin D levels (<30 ng/mL) were more prone to recent upper respiratory infections compared to those with higher vitamin D levels, even after adjusting for variables like season, age, gender, weight, and race (Walker & Modlin, 2009). Rigorous double-blind placebo studies with objective outcomes, such as nasopharyngeal swab cultures (not self-reported), and therapeutic doses of vitamin D have demonstrated a statistically significant reduction (42%) in the incidence of influenza infection (Van de Peppel & van Leeuwen, 2014; Holick, 2018). The positive impact of vitamin D on protective immunity is attributed in part to its influence on the innate immune system. Macrophages, upon recognizing lipopolysaccharide (LPS) through toll-like receptors (TLR), initiate a cascade leading to the production of potent bactericidal peptides like Cathelicidin and defensing (Carmeliet etb al., 2015). These peptides localize with damaged bacteria in the phagosome, effectively destroying bacterial cell membranes and exhibiting strong antibacterial activity. Vitamin D plays a vital role in the innate antibacterial response by increasing the expression of 1-α-hydroxylase and VDR upon TLR binding (Hanel & Carlberg, 2020). This prompts the 1,25 D-VDR-RXR heterodimers to bind to vitamin D response elements of Cathelicidin and beta-defensin 4 genes and transcribe these proteins. Recent studies further confirm that calcitriol has direct effects on B cell homeostasis, inhibiting memory and plasma cell formation and promoting apoptosis of B cells producing immunoglobulin. The control of B cell activation and proliferation holds significant clinical relevance in autoimmune diseases where B cells producing autoreactive antibodies contribute to pathophysiology. Calcitriol can inhibit the proliferation and differentiation of T helper cells, regulating helper T cells (Th) and cytokines (Hewison,

2012). Specifically, treatment with calcitriol or analogs inhibits pro-inflammatory cytokines Th1 (IL2, interferon-, tumor necrosis factor α), Th9 (IL9), and Th22 (IL22) (Özkan, 2010). Cytokine secretion further suppresses the production of inflammatory Th2 cytokines (IL3, IL4, IL5, IL10)49. Vitamin D also affects Th17 cells producing IL17, playing a pivotal role in the treatment of autoimmune diseases such as obese diabetic mice (NOD) (Hanel & Carlberg, 2020).

4. Unani Concept of Immunity

According to the Unani Medical concept, nature bestows the power to preserve health, deploying innumerable systems and control mechanisms at the cellular, tissue, and whole-body levels. Some functions operate within cells, others between cells, and additional functions span the entire body to sustain health (Lu et al., 2019). The renowned Unani scholar Ali Bin RabbanTabri, in his work FirdousalHikmat, posited that "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), QuwwateHaiwania (Vital Faculty), and QuwwateNafsania (Nervous Faculty)". Thus, the primary role of Tabiyat is to provide general management and defense, or immunity, against external threats. Tabiat encompasses the collective human structure, function, and psychological characteristics. Hippocrates postulated that every individual possesses a unique ability termed the body's defense mechanism, expressed in Unani as Tabiat Muddabare Badan. This Tabiat is considered the best physician, maintaining the equilibrium of the body's four humors (Weick, 1967). To preserve health, adjustments in quantity and body fluids must align with the quality of the body's natural chemical components. Tabiat or the efficacy of Quwwat-e-Muddabira Baden is influenced by various exogenous and endogenous factors. Tabiyat-e-Insaniah governs all biochemical processes and physiological functions of the human body, safeguarding Aetidal Mizaj (Vintilescu et al., 2019). Unani Medicine contends that diet and regimens can enhance health, prevent, and treat diseases. In this holistic medical system, fortifying Tabiat (immunity) through immunomodulators, maintaining a balanced temperament, upholding a humorous equilibrium of quality and quantity, adhering to the AsbabeSittaZarooriya (six essential elements of life), and adopting maddiwa gair madditadabeer (i.e., regimenal therapy and counseling) and MunzijwaMushil (concoctive and purgative) therapy, as well as Ilajbilghiza (Dieto-therapy), are deemed the most effective approaches (Carmeliet etb al., 2015). Zakaria Razi articulated in "Kitabul Murshid" that "Tabiat relieves diseases and expels waste materials from the human body and living beings" (Van de Peppel & van Leeuwen, 2014). The existence of Tabiat becomes apparent in instances such as the spontaneous healing of minor wounds without intervention and the improvement or cure of various pains and diseases following rest or over time (Hewison, 2012). All these phenomena emanate from the administrative and managerial prowess of Tabiat. Life-associated functions such as regeneration, growth, and development manifest solely in living bodies, with corpses lacking renewal capabilities and responsiveness to any form of medicine due to the absence of Tabiat. Regimental therapy (Ilaj-bil-tadbeer) stands as one of the most revered treatment methods, embraced by ancient Unani scholars since time immemorial. Essentially, the application of specific techniques or physical methods enhances the body's structure by eliminating waste and augmenting the body's defense mechanism. Fasd (blood draw/puncture), Ta'aleeq (hirudotherapy), and Hijaamat (cupping) constitute integral components of this therapeutic approach. Ibn-e-Sina, a distinguished Unani scholar, documented in his seminal work "Canon of Medicine" that nearly 36 regimens exist, with "hammam" among the beneficial regimes for boosting immunity. The "Hammam" (Turkish bath), also known as the healing bath, represents one of the earliest Unani therapies employed for certain diseases. The bathhouse, designed with specific rooms catering to individualized conditions based on the targeted ailment, has been a staple in Unani treatment. Aside from its various benefits, Hammam reinforces the body's immunity against specific diseases. Similar to Riyazat and Dalq, Hammam falls under the category of Asbab-e- GhairZaroriya, indicating that these practices are not essential for survival but contribute to health when executed under suitable conditions. The comprehensive integration of Turkish baths with dietary and exercise measures activates the immune system and enhances overall health (Van de Peppel & van Leeuwen, 2014; Holick, 2018).

4.1 Hammam Shamshi (Sunbathing)

In this scenario, the body is exposed directly to sunlight.

4.2 Benefits and Use

Sunlight serves as a source of vitamin D3, crucial for enhancing bone strength through improved calcium absorption. Generally recommended is spending 15-30 minutes in direct sunlight during the morning (Lu et al., 2019).

5. Conclusion

Recent research underscores a robust connection between vitamin D and body immunity, spanning both innate and adaptive immunity. Across extensive tissues, every body cell, including immune cells, features nuclear VDR expression and possesses an enzyme metabolizing vitamin D, enabling the local, autocrine, and paracrine conversion of provitamin D 25 D into the active form of vitamin D, namely calcitriol or D3. This process proves indispensable for immune function, and thus, compromised or inadequate vitamin D levels may diminish immune capabilities. This underscores the potential of vitamin D supplementation in influencing the trajectory of autoimmune diseases. However, uncertainties persist regarding the optimal serum level for initiating vitamin D supplementation and the effective dosage form (D2 or D3). Addressing these questions necessitates future extensive clinical studies.

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