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Vitamin D Receptor Renewal Through Anti-inflammatory Diet

(Another Contributing Factor for Vitamin D Resistance)

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By: Eduardo Patrick Beltran M.
Internal Medicine - Dermatology
Director of Clinical Research SPIMS
Research Scientist – Vitamin D Expert
dr.beltran@spinstitute-ms.com

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Vitamin D Receptor Renewal Through Anti-inflammatory Diet

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By: Eduardo Patrick Beltran M. MD
dr.beltran@spinstitute-ms.com

ABSTRACT

Vitamin D is an essential nutrient that plays a crucial role in maintaining bone health, immune function, and overall health. Adequate levels of vitamin D are important for proper calcium absorption, regulation of gene expression, and modulation of immune responses. However, patients with autoimmune diseases may have genetic polymorphisms that contribute to vitamin D resistance, such as single nucleotide polymorphisms (SNPs) affecting the genes CYP2R1, CYP27B1, VDR, and VDBP.

In addition, these patients may have ongoing leaky gut syndrome due to inflammatory foods, such as gluten, dairy, lectins, and sugars, which can lead to molecular mimicry and the production of autoantibodies. This condition sets the stage for foreign proteins and toxins, including lipopolysaccharides, endotoxins, exotoxins, and mycotoxins, to enter the bloodstream, further inducing the production of autoantibodies.

Bacterial, fungal, and viral infections can also contribute to vitamin D resistance by downregulating the expression of vitamin D receptors, and this mechanism is often overlooked. For instance, studies have shown that some viruses, such as HIV, HSV1, HCV, and EBV, can suppress VDR expression and vitamin D signaling pathways, leading to decreased immune response and increased viral replication

Understanding the mechanisms by which these toxins and infections impact vitamin D receptor expression, end up creating a contributing factor for vitamin D resistance that is sometimes overlooked on behalf healthcare providers. Additionally, we have learned a great deal from high dose vitamin D therapy supplementation alongside anti-inflammatory dietary which has been shown to reduce degree of dysbiosis and intestinal permeability giving time for our cells to in order to upregulate VDRs in our immune cells and restore our immunologic tolerance once again.

INTRODUCTION

Vitamin D is a crucial nutrient that plays an important role in maintaining bone health, regulating immune function, and reducing the risk of several chronic diseases. However, despite its critical importance, vitamin D deficiency is highly prevalent across the world, affecting millions of people, particularly those living in areas with limited sun exposure or with dietary restrictions [1]. This deficiency has been linked to a range of health conditions, including autoimmune diseases, which are characterized by the body's immune system attacking its own healthy tissues and organs [2,3,4,5].

The link between vitamin D deficiency and autoimmunity has been extensively studied, with several mechanisms proposed to explain the association. Vitamin D deficiency is thought to promote autoimmunity by impairing the function of immune cells, including regulatory T cells and dendritic cells, which play a critical role in maintaining immune homeostasis and preventing autoimmune responses [6]. Additionally, vitamin D deficiency has been linked to increased production of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-alpha), which can further exacerbate autoimmune responses.

Moreover, vitamin D deficiency has been shown to contribute to the development of leaky gut syndrome, a condition in which the lining of the intestines becomes more permeable, allowing foreign proteins and toxins to enter the bloodstream, inducing the production of autoantibodies, and ultimately leading to autoimmune disease [7,8].

Given the critical role of vitamin D in maintaining immune health and preventing autoimmunity, understanding the causes and consequences of vitamin D deficiency is essential for developing effective prevention and treatment strategies for autoimmune diseases.

VITAMIN D PHYSIOLOGY & POLYMORPHISMS

Vitamin D is an essential nutrient that is critical for maintaining bone health and supporting many other physiological processes in the body. It exists in several different forms, with the most biologically active form being 1,25-dihydroxyvitamin D (calcitriol). The process of converting vitamin D from its inactive forms to its active form involves several steps, each with its own half-life [9].

The first step in this process is the synthesis of vitamin D in the skin upon exposure to UVB radiation. This form of vitamin D, known as cholecalciferol, has a very short half-life of approximately 1-2 days in the blood. Cholecalciferol is then transported to the liver, where it is converted to 25-hydroxyvitamin D (calcifediol). Calcifediol has a longer half-life of approximately 2-3 weeks in the blood, making it a more reliable indicator of vitamin D status [10].

From the liver, calcifediol is transported to the kidneys, where it is converted to calcitriol, the biologically active form of vitamin D. Calcitriol has a half-life of approximately 4-6 hours in the blood, but it is highly potent and can interact with vitamin D receptors (VDRs) throughout the body [10].

VDRs are found in many different tissues and cell types, including bone, muscle, immune cells, and the intestines. The action of calcitriol on VDRs can occur through several different pathways, including autocrine, intracrine, paracrine, and endocrine signaling [11].

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Autocrine signaling refers to the action of vitamin D within the same cell that produced it. In this pathway, vitamin D is synthesized within a cell and then acts on VDRs within that same cell to regulate gene expression and cellular processes [11,12,13].

Intracrine signaling involves the action of vitamin D within a nearby cell or tissue. In this pathway, vitamin D is synthesized within one cell type and then transported to a neighboring cell, where it can act on VDRs to influence cellular processes [11,12,13].

Paracrine signaling involves the action of vitamin D on a distant cell or tissue. In this pathway, vitamin D is synthesized and released into the bloodstream, where it can then travel to other tissues and organs to act on VDRs [11,12,13].

Endocrine signaling involves the systemic action of vitamin D on multiple tissues and organs throughout the body. In this pathway, vitamin D is synthesized in the skin or ingested through the diet, and then transported to the liver and kidneys, where it is converted to calcitriol. Calcitriol is then released into the bloodstream and acts on VDRs throughout the body to regulate a wide range of physiological processes [11,12,13].

There are also several different forms of ***vitamin D polymorphism*** that can affect the metabolism and activity of vitamin D. These include **CYP2R1**, which is involved in the initial conversion of cholecalciferol to calcifediol in the liver; **CYP27B1**, which is involved in the conversion of calcifediol to calcitriol in the kidneys; **VDBP**, which is a protein that transports vitamin D in the blood; and VDR, which is the receptor that mediates the action of vitamin D in cells and tissues throughout the body [14,15,16]. Variations in these polymorphisms can affect vitamin D status and increase the risk of certain health conditions.

MICROBIOME: DYSBIOSIS/SIBO/SIFO/BIOFILMS

The gut microbiome is a complex community of microorganisms that live in our digestive tract, playing a critical role in maintaining our health. When this community is in a state of balance and harmony, it is referred to as eubiosis [17]. Eubiosis is essential for the proper functioning of the digestive system, the immune system, and even the brain. However, when this delicate balance is disrupted, dysbiosis can occur, which can lead to a range of health problems.

Dysbiosis refers to a state of microbial imbalance in the gut, where there is an overgrowth of harmful bacteria and a decrease in beneficial bacteria [18]. This can be caused by several factors, including poor diet, stress, infections, and the use of antibiotics. When dysbiosis occurs, it can disrupt the proper functioning of the digestive system, leading to a range of gastrointestinal problems, including SIBO and SIFO.

SMALL INTESTINAL BACTERIAL OVERGROWTH

Small intestinal bacterial overgrowth (SIBO) is a condition in which there is an overgrowth of bacteria in the small intestine. The small intestine normally contains relatively low levels of bacteria, while the majority of the gut bacteria reside in the large intestine. However, in cases of SIBO, bacteria from the large intestine migrate upward into the small intestine and multiply to excessive levels.

There are several factors that can contribute to the development of SIBO. One of the primary causes is impaired motility of the small intestine. This can be due to conditions such as gastroparesis or intestinal dysmotility [19], which can slow down the movement of food and fluids through the gut. This can lead to an accumulation of bacteria in the small intestine and increase the risk of overgrowth.

Another factor that can contribute to SIBO is a disruption of the normal balance of gut bacteria. This can be caused by various factors such as antibiotic use, proton pump inhibitors (PPIs), or other medications that can alter the gut microbiome [20]. Stress, poor diet rich in foods such as; gluten, dairy, lectins and sugars (processed foods) and other lifestyle factors (stress) can also contribute to dysbiosis and increase the risk of SIBO.

Additionally, certain underlying health conditions can increase the risk of SIBO. These include conditions such as inflammatory bowel disease, celiac disease, and pancreatic insufficiency, which can affect the normal functioning of the gut and lead to bacterial overgrowth.

Once an overgrowth of bacteria occurs in the small intestine, these bacteria can produce various toxins and metabolites that can damage the gut lining and lead to increased permeability. This can allow bacterial toxins, such as lipopolysaccharides (LPS), endotoxins, and exotoxins, to enter the bloodstream and interact with the immune system, potentially leading to inflammation and autoimmunity [21,22,23,24].

SIBO: LIPOPOLYSACHARIDES & VDR's

LPS, also known as endotoxins, are molecules found in the outer membrane of gram-negative bacteria, and they can trigger a potent immune response when they enter the bloodstream. Exotoxins, on the other hand, are toxins released by bacteria into the environment, and they can also cause damage to host tissues. One of the ways in which LPS can affect the body is by downregulating vitamin D receptors (VDR) [25,26].

VDR is a nuclear receptor that plays a crucial role in the regulation of calcium and phosphorus metabolism, immune function, and cell differentiation. When activated by vitamin D, VDR can regulate the expression of genes involved in these processes.

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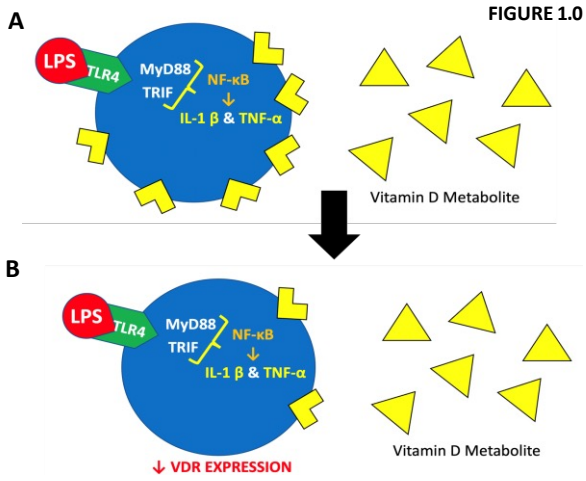
However, LPS can interfere with the activation of VDR by several mechanisms. One of the primary ways is through the activation of toll-like receptor 4 (TLR4), a receptor that recognizes LPS and triggers an inflammatory response. TLR4 activation via MyD88 & TRIF pathways (Figure 1.0) that can lead to the activation of nuclear factor kappa B (NF-κB) that induces the production of IL-1 & TNF alfa, transcription factors that can inhibit VDR expression by binding to the VDR promoter region [25].

FIGURE 1.0



In (image A) show normal VDR expression, but when exposed to LPS, NFkB (image B) induces the production of IL-1B & TNF alfa which downregulates VDR expression in all immune cells.

Additionally, LPS can also increase the expression of CYP24A1 (24 hydroxylase), an enzyme that breaks down the active form of vitamin D, 1,25-dihydroxyvitamin D (calcitriol), into an inactive metabolite. This can lead to a decreased availability of calcitriol, which is required for the activation of VDR [26].

Furthermore, LPS can also affect the activity of VDR by altering the expression of co-regulators that interact with VDR. For example, LPS can increase the expression of histone deacetylases (HDACs) [27], which can reduce VDR activity by removing acetyl groups from histones and making the chromatin structure less accessible for VDR binding.

Chronic exposure to LPS and other bacterial toxins can also lead to a state of chronic low-grade inflammation, which is contained in part thanks to , which has been associated with the development of autoimmune diseases [28]. This may occur through several mechanisms, including the activation of autoreactive T cells, the production of autoantibodies, and the dysregulation of regulatory T cells and B cells [29].

In essence, SIBO can lead to an increased entry of bacterial toxins into the bloodstream, which can activate immune cells and cause inflammation and tissue damage. This chronic inflammation can also contribute to the development of autoimmune diseases through various mechanisms.

SIBO: LIPOPOLYSACHARIDE CLEARANCE

Excessive LPS levels in the bloodstream can lead to inflammation and various diseases, such as sepsis, metabolic disorders, and autoimmune diseases. Therefore, the body has developed mechanisms to control circulating LPS levels and prevent their harmful effects.

One of the mechanisms used to control LPS levels is the binding of LPS to lipoproteins. High-density lipoprotein (HDL), low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL) are known to bind LPS and remove them from circulation. HDL, in particular, has a high affinity for LPS and has been shown to be a major LPS-binding protein in the bloodstream [30]. By binding to LPS, HDL can neutralize its inflammatory effects and promote its clearance from circulation (Figure 1.3).

VLDL and LDL, on the other hand, have lower LPS-binding capacity compared to HDL but can still play a role in LPS metabolism. These lipoproteins can bind to LPS and transport them to the liver for metabolism and elimination [31].

Lipopolysaccharide-binding proteins (LBP) are another type of protein that can control LPS levels. LBP binds to LPS and facilitates its transfer to immune cells, which can trigger an inflammatory response. However, LBP can also promote LPS clearance by facilitating its uptake and transport to the liver for metabolism [32, 33].

Once LPS is taken up by the liver, it undergoes hepatic metabolism, which involves several enzymes that can break down and detoxify LPS. For instance, **acyloxyacyl hydrolase (AOAH)** can remove *the* **lipid A portion of LPS**, which is responsible for its toxicity. In addition, **LBP-related protein (LRP)** can also help in LPS clearance by binding to and neutralizing LPS in the liver [34].

Overall, lipoproteins and LBP play critical roles in controlling LPS levels and preventing excessive LPS-induced inflammation and disease. These proteins bind to LPS and transport it to the liver for metabolism and elimination. The liver, in turn, is responsible for detoxifying LPS and removing it from circulation. This intricate interplay between lipoproteins, LBP, and the liver is essential for maintaining a healthy immune system and preventing LPS-induced diseases [34].

SMALL INSTESTINAL FUNGAL OVERGROWTH

Small Intestinal Fungal Overgrowth (SIFO) is a condition in which there is an overgrowth of fungi in the small intestine. The fungi commonly associated with SIFO include Candida albicans, Candida tropicalis, Candida glabrata, and Aspergillus fumigatus. Among these, Candida albicans is the most commonly identified fungi in SIFO cases.

Candida albicans is an opportunistic fungus that normally resides in the human gut, but can cause infections when its growth is not properly controlled. Candida albicans produces a toxin called **candidalysin**, (Figure 1.1) which can damage the intestinal lining and promote inflammation [35]. This damage can lead to nutrient malabsorption and contribute to the development of digestive symptoms. In addition to candidalysin, several other mycotoxins have been identified that can downregulate vitamin D receptors in the small intestine. These mycotoxins include:

Ochratoxin A: This mycotoxin is produced by Aspergillus and Penicillium fungi and is commonly found in contaminated food. Ochratoxin A has been shown to reduce the expression of vitamin D receptors in intestinal epithelial cells, leading to decreased calcium absorption and increased intestinal permeability [36].

Aflatoxin B1: This mycotoxin is produced by the Aspergillus flavus and Aspergillus parasiticus fungi and is commonly found in peanuts, corn, and other grains. Aflatoxin B1 has been shown to reduce the expression of vitamin D receptors in liver cells, which can contribute to liver damage and dysfunction [37].

Zearalenone: This mycotoxin is produced by Fusarium fungi and is commonly found in grains, such as corn, wheat, and barley. Zearalenone has been shown to reduce the expression of vitamin D receptors in human breast cancer cells, which may contribute to the development of breast cancer [38].

Deoxynivalenol (DON): This mycotoxin is also produced by Fusarium fungi and is commonly found in wheat, barley, and corn. DON has been shown to reduce the expression of vitamin D receptors in human intestinal epithelial cells, which can contribute to intestinal inflammation and damage [39].

T-2 toxin: This mycotoxin is produced by the Fusarium fungi and is commonly found in grains, such as wheat, oats, and barley. T-2 toxin has been shown to reduce the expression of vitamin D receptors in human lung cells, which can contribute to respiratory problems and immune dysfunction [40].

In general, SIFO is a condition in which there is an overgrowth of fungi in the small intestine, and Candida albicans is the most commonly identified fungus in SIFO cases. Candidalysin is a toxin produced by Candida albicans that can damage the intestinal lining and contribute to inflammation. In addition, several mycotoxins, including candidalysin, ochratoxin A, aflatoxin B1, zearalenone, deoxynivalenol, and T-2 toxin, can downregulate vitamin D receptors in the small intestine, which can contribute to nutrient malabsorption and immune dysfunction.

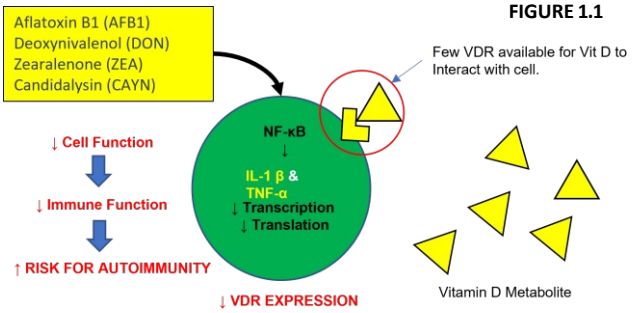


FIGURE 1.1

In this figure we can appreciate how mycotoxins can downregulate the expression of vitamin D receptors via NFkB pathway which induces the production of IL-1B & TNF alfa. A similar mechanism when compared to endotoxins.

BIOFILMS

Biofilms are another factor that can contribute to dysbiosis and the development of SIBO and SIFO. Biofilms are formed by communities of microorganisms that adhere to surfaces and are surrounded by a ***matrix of extracellular polymeric substances (EPS).***

The process by which microorganisms communicate with each other to form a matrix of extracellular polymeric substances (EPS) and eventually biofilms is known as quorum sensing. Quorum sensing is a mechanism of cell-to-cell communication that allows microorganisms to coordinate their behavior and respond to changes in their environment. It involves the production and detection of signaling molecules known as autoinducers [41].

The first step in quorum sensing is the production of autoinducers by the microorganisms. Autoinducers can be small molecules such as acyl homoserine lactones (AHLs) in bacteria or oligopeptides in fungi. As the microorganisms grow and replicate, the concentration of autoinducers in the environment increases [42].

When the concentration of autoinducers reaches a threshold level, the microorganisms can detect them using specific receptors. The binding of the autoinducer to its receptor triggers a signaling cascade within the microorganism, leading to changes in gene expression and behavior.

In the case of biofilm formation, quorum sensing allows the microorganisms to coordinate the production of EPS and the organization of the biofilm. EPS production is a complex process involving the synthesis and secretion of various polysaccharides, proteins, and nucleic acids. Quorum sensing regulates the expression of genes involved in EPS production, allowing the microorganisms to produce the appropriate mix of polymers for the biofilm matrix.

Once the EPS matrix is established, the microorganisms can organize themselves within the biofilm and differentiate into specialized subpopulations.

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For example, some cells may be responsible for producing enzymes to break down nutrients, while others may be involved in motility or sensing environmental cues.

Overall, quorum sensing is a key mechanism by which microorganisms communicate and coordinate their behavior. In the case of biofilm formation, quorum sensing allows microorganisms to produce the EPS matrix and organize themselves within the biofilm, leading to increased resistance to antibiotics and host immune responses.

Biofilm formation can occur in various parts of the body, including the skin, oral cavity, urinary tract, respiratory tract and especially gastrointestinal tract. The process of biofilm formation (Figure 1.2) in the body typically involves the following steps:

1. **Attachment:** Microorganisms attach to a surface, such as a tissue or implanted medical device, using adhesion molecules on their cell surface [43].

2. **Colonization:** Microorganisms begin to grow and divide on the surface, forming a microcolony [43].

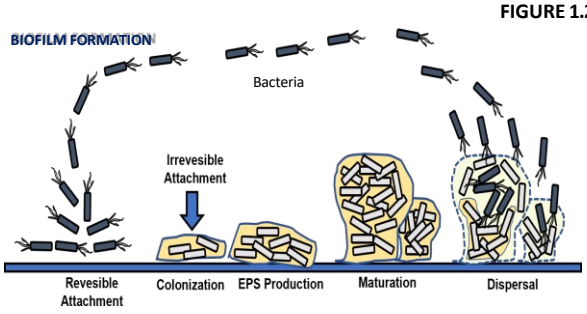
3. **EPS production:** Microorganisms produce EPS, which creates a protective matrix around the microcolony and helps to anchor it to the surface [43].

4. **Maturation:** The biofilm continues to grow and mature, with the microorganisms in the biofilm communicating with each other through quorum sensing [43].

5. **Dispersal:** In some cases, the biofilm may disperse, releasing individual microorganisms into the surrounding environment [43].

Factors that can contribute to biofilm formation in the body include the presence of foreign objects, such as catheters or implants, as well as changes in the body's immune system, which can be attributed to vitamin D deficiency and changes to the GI microbiome. Once a biofilm is formed, it can be difficult to treat with conventional antibiotics or other therapies, as the EPS matrix protects the microorganisms from the immune system and inhibits the penetration of drugs [44].

FIGURE 1.2



In this figure we can appreciate the five steps involved in the formation of biofilms:
1.) Reversible Attachement 2.) Colonization 3.) EPS production 4.) Maturation 5.) Dispersal.

VIRAL INFECTIONS & VDR

Viral infections can have a significant impact on the expression of vitamin D receptors (VDRs) in the human body. This is particularly true for infections caused by the human immunodeficiency virus (HIV), herpes simplex virus type 1 (HSV1), hepatitis C virus (HCV), and Epstein-Barr virus (EBV). The mechanism underlying this interference is multifactorial and can have severe consequences on the immune system [45].

The VDR is a transcription factor that plays a crucial role in the regulation of several biological processes, including calcium homeostasis, bone metabolism, and immune function. It is present in most tissues, including immune cells such as T cells, B cells, and macrophages. Once activated, the VDR binds to specific DNA sequences, regulating the expression of target genes.

Several studies have shown that viral infections can decrease the expression of VDR in immune cells. For example, HIV infection has been shown to downregulate the expression of VDR in CD4+ T cells, leading to impaired immune function. Similarly, HSV1 infection has been shown to reduce the expression of VDR in human corneal epithelial cells, leading to a decrease in the production of antimicrobial peptides and an increase in viral replication [46, 47].

The hepatitis C virus (HCV) is also known to interfere with VDR expression. In HCV-infected patients, a decrease in VDR expression has been observed in peripheral blood mononuclear cells, leading to a reduction in immune response and an increased risk of HCV-related complications [48].

Moreover, the Epstein-Barr virus (EBV) has been shown to decrease VDR expression in B cells, leading to a decrease in the production of antimicrobial peptides and an increase in viral replication [49].

The mechanism behind the interference of viral infections with VDR expression is not entirely clear. It is hypothesized that viral proteins may directly interact with the VDR or its ligand, 1,25-dihydroxyvitamin D3, leading to its degradation or inhibiting its activity. Additionally, the proinflammatory cytokines released during viral infections, such as interferon-gamma and tumor necrosis factor-alpha, can also downregulate VDR expression [50].

In summary, viral infections can significantly impact the expression of VDR, leading to a decreased immune response and an increased risk of viral replication and related complications. Therefore, it is crucial to monitor VDR expression in patients with viral infections to identify those at risk of immune dysfunction and to develop targeted therapeutic interventions to enhance immune function.

ANTI-INFLAMMATORY DIET

The modern Western diet is high in processed foods, refined sugars, and carbohydrates that have been linked to numerous health problems, including obesity, diabetes, and autoimmune diseases. In particular, gluten, dairy, lectins (such as those found in nightshades), and sugars have been found to have a detrimental impact on the gastrointestinal (GI) lining, affecting tight junctions and increasing gut permeability [51,52,53].

Tight junctions are critical to maintaining the integrity of the GI lining, which acts as a barrier between the inside of the body and the outside environment. When tight junctions are compromised, toxins and other harmful substances can leak into the bloodstream, leading to inflammation and other health problems. Gluten, dairy, lectins, and sugars have all been found to increase gut permeability by compromising tight junctions in the GI lining [54,55].

Gliadin, a wheat-derived lectin, has been shown to upregulate the synthesis of zonulin in the intestinal epithelium. Zonulin is a protein that regulates the tight junctions between enterocytes, which are responsible for maintaining the integrity of the gut barrier. When zonulin is upregulated, the tight junctions between enterocytes become looser, leading to increased permeability of the gut barrier [55].

This increased gut permeability can lead to the passage of undigested food particles and other antigens into the bloodstream, overwhelming our immunologic tolerance and leading to an autoimmune response. Molecular mimicry can occur when the immune system mistakes self-antigens for foreign antigens and attacks the body's own tissues [56,57,58]. This can result in autoimmune diseases such as celiac disease, in which the immune system attacks the lining of the small intestine.

In addition to the effects of gliadin, many foods today, including wheat and many other cereals, are treated with glyphosate. Glyphosate is a known carcinogen and can also break down the tight junctions in the intestinal epithelium, further increasing gut permeability. Glyphosate also has a patent for being an antibiotic, which can kill off the natural microbiome in our gut, affecting our microbiome diversity and causing a disruption in the population of bifidobacterial [59,60,61].

Bifidobacteria are responsible for producing fatty acid chains that are necessary for the health of our goblet cells, which produce the mucin layer that separates the microbiome from interacting with our immune system. Killing off bifidobacteria can directly affect the mucin layer and contribute to autoimmune diseases [62].

Consuming wheat derived foods will cause upregulation of zonulin synthesis by gliadin and the use of glyphosate in food production can both contribute to increased gut permeability, disrupting the microbiome and mucin layer, and leading to autoimmune diseases through molecular mimicry.

The anti-inflammatory diet that excludes these foods (gluten, dairy, lectins and sugars) can greatly reduce the entry of bacterial toxins (such as LPS and endotoxins) and fungal toxins into the bloodstream. This, in turn, can allow for the restoration of gut lining integrity and the renovation of enterocyte lining. This process typically takes several weeks to several months in order to restore gut lining integrity, depending on the severity of damage [63].

Vitamin D has been found to play a role in protecting tight junction integrity, and its deficiency has been linked to increased intestinal permeability. The reduction of inflammation that comes with an anti-inflammatory diet can allow for cells to once again express more vitamin D receptors on their surface, which allows for adequate vitamin D metabolite binding to its receptor [64].

Avoiding gluten, dairy, lectins, and sugars in an anti-inflammatory diet can help reduce gut permeability and improve gut lining integrity. This can lead to the reduction of toxins entering the bloodstream and the restoration of enterocyte lining. Vitamin D also plays a role in protecting tight junctions, and its adequate intake is essential for gut health.

BIOFILM DISRUPTORS

While an anti-inflammatory diet and high dose vitamin D therapy can be effective for many patients, some may be refractory to these treatments alone. This is where the use of herbal antimicrobials as biofilm disruptors can be particularly valuable.

Herbal antimicrobials have been used for centuries to treat a wide range of infections and diseases. Many of these natural substances have been shown to have potent antimicrobial activity against a variety of pathogens, including bacteria and fungi. What's more, some herbal antimicrobials have been specifically shown to be effective at disrupting biofilms [65,66,67].

For example, studies have shown that essential oils derived from plants like oregano, thyme, and tea tree can effectively penetrate and disrupt biofilms formed by a variety of pathogenic bacteria, including those associated with SIBO and SIFO. Other herbal antimicrobials like oregano oil, berberine and allicin (found in garlic) have also been shown to be effective biofilm disruptors [68,69].

By incorporating these herbal antimicrobials into a comprehensive treatment plan that also includes dietary and lifestyle modifications, patients with SIBO, SIFO, or other biofilm-associated conditions have been able to achieve better outcomes in our practice than with

anti-inflammatory diet and high dose vitamin D therapy alone.

It is extremely important to work with a healthcare provider who is knowledgeable in the use of herbal antimicrobials and can help develop an individualized treatment plan based on each patient's unique herbal needs. In our practice the use of herbal antimicrobials as biofilm disruptors has been seen to be a safe and effective way in overcoming chronic infections and reducing autoimmunity.

LIVER METABOLISM: ALPHA LIPOIC ACID & VDR

The liver is one of the most important organs in the body when it comes to detoxification. It plays a crucial role in metabolizing and eliminating toxins, LPS, and viruses from the body. This process involves two distinct phases known as phase 1 and phase 2 metabolism. These phases work together to convert these harmful substances into water-soluble compounds that can be excreted from the body [70].

Phase 1 metabolism is the first step in the detoxification process. During this phase, enzymes in the liver, known as cytochrome P450 enzymes, break down toxins and other harmful substances into smaller molecules. These molecules are then prepared for phase 2 metabolism.

Phase 2 metabolism is the second step in the detoxification process. This phase involves a variety of enzymatic reactions that conjugate the phase 1 metabolites with molecules such as glutathione, sulfate, and glucuronic acid. These conjugated metabolites are then excreted from the body through urine or bile.

Alpha lipoic acid is a powerful antioxidant that plays a crucial role in the liver's detoxification process. It is involved in both phase 1 and phase 2 metabolism. Alpha lipoic acid is a co-factor for many enzymes involved in phase 1 metabolism, including the cytochrome P450 enzymes. It helps to increase the activity of these enzymes, thereby improving the liver's ability to break down toxins and other harmful substances [71].

Alpha lipoic acid also plays an essential role in phase 2 metabolism. It is a co-factor for many phase 2 enzymes, including glutathione S-transferases, which are responsible for conjugating the phase 1 metabolites with glutathione [72].

This process is critical for the elimination of toxins from the body, as glutathione is a potent antioxidant that helps to protect cells from oxidative stress and damage.

Studies have shown that alpha lipoic acid supplementation can improve liver function and increase the liver's ability to detoxify harmful substances. It has been shown to reduce liver inflammation, improve liver regeneration, and protect against liver damage caused by toxins, viruses, and LPS [73].

Furthermore, alpha lipoic acid has been found to have an immune-enhancing effect, which can be beneficial for individuals who are dealing with viral infections. It has been shown to increase the activity of immune cells, including T cells and B cells, which are responsible for fighting off infections [74].

Additionally, alpha lipoic acid has been shown to have antiviral properties. It has been found to inhibit the replication of viruses, including HIV, hepatitis C, and influenza. Alpha lipoic acid can disrupt the virus's ability to replicate and spread by interfering with the virus's ability to bind to host cells and enter them [75, 76, 77].

Furthermore, alpha lipoic acid has been shown to reduce inflammation caused by viral infections. Inflammation is a natural immune response to viral infections, but excessive inflammation can lead to tissue damage and worsen the symptoms of the infection. Alpha lipoic acid can reduce inflammation by inhibiting the production of pro-inflammatory cytokines [78].

In summary, alpha lipoic acid can reduce viral load by enhancing the immune response against viral infections, inhibiting viral replication, and reducing inflammation caused by viral infections.

Alpha-lipoic acid (ALA) has been shown to have a variety of beneficial effects by increasing significantly glutathione levels in the body [79]. Glutathione has been shown to increase 25-hydroxyvitamin D (25OHD3). Adequate glutathione status in the liver upregulates vitamin D regulatory genes, which activates vitamin D [80].

By introducing ALA and glutathione we are able to upregulate vitamin D converting enzymes and CYP450 enzymes that have an important role in liver metabolism and aiding in the elimination of different forms of toxins, LPSs, endotoxins, exotoxins, mycotoxins and many heavy metals.

Patients who received ALA as a cofactor alongside a HDVD + AID a modified version of the Coimbra Protocol [82] in our practice have shown to have better outcomes when compared to those who do only take HDVD + AID. This is perhaps due to better liver function elimination of toxins and increase in bioavailability of vitamin D metabolites.

In addition, ALA when combined has greatly helped our obese patients with insulin resistance and diabetes restore their HA1C levels within normal reference range much faster when compared to the patients who only did HDVD + AID. ALA has certainly made a big difference in improving liver functions in our patients and is now included as part of the LGS Protocol (Beltran MD, E) [63].

Further more lipid profiles and inflammatory biomarkers (CRP, NF-kB, ICAM-1, VCAM-1, MMP-2, MMP-9, and IL-6) [83,84,85] improved faster in patients who took HDVD+AID+ALA vs HDVD+AID. Since ALA is a powerful antioxidant that improves endotoxemia clearance through various mechanisms by reducing oxidative stress (free radical scavenger), immune modulation (TNF alfa & IL-6 reduction), enhancing liver function clearance and by restoring mitochondrial function. It clearly makes sense implementing ALA as an important cofactor that helps restore liver metabolism in autoimmune patients.

HDVD + AID & BIOFILM DISRUPTORS

Autoimmune diseases occur when the immune system attacks healthy cells in the body, leading to chronic inflammation and tissue damage. Conventional treatment often involves the use of immunosuppressive drugs, which can have many negative side effects. However, recent research suggests that a combination of high-dose vitamin D (HDVD) therapy and an anti-inflammatory diet may be a promising approach for treating autoimmune diseases.

One of the key components of this approach is the removal of pro-inflammatory substances from the diet, such as gluten, dairy, lectins (found in nightshades), and sugars. These substances can increase gut permeability and disrupt the microbiome, leading to chronic inflammation in the body. By eliminating these substances, patients can experience significant improvements in their symptoms in a short period of time.

However, HDVD therapy is also an essential part of this approach. Many autoimmune patients have vitamin D polymorphisms, which can make it difficult for their bodies to absorb and utilize vitamin D effectively. Increasing the dosage of vitamin D can compensate for these polymorphisms and help to reduce inflammation in the body.

To ensure the effectiveness of HDVD therapy, patients need to take several co-factors such as magnesium, vitamin K2 (mk7), and the methylated forms of B9 and 12 vitamins and other B vitamins that support the methylation cycle. Omega 3, curcumin, royal jelly are cofactors that aid in liver metabolism and help to maintain tight junction integrity in the gut.

The LGS protocol, created by Dr. Beltran [63], implements in part the use of L-glutamine, licorice, and aloe vera extract which supports maintaining enterocyte tight junction integrity. In addition, supplements such as alpha-lipoic acid, selenium, copper, zinc, and boron are essential for liver metabolism. **More than 25 cofactors are used in the protocol.**

Despite the effectiveness of this protocol, there are a group of refractory patients that do not respond as well to HDVD + AID. These patients have a common denominator of moderate to severe degree of dysbiosis that is caused by the presence of SIBO, SIFO, or biofilms.

Such conditions at times require the use of biofilm disruptors (Figure 1.4 A & 1.4B). Biofilm disruptors are herbal antimicrobials that are effective in breaking down the protective barrier that bacteria and fungus use to evade immune system detection and survive antimicrobial agents.

One of the most effective biofilm disruptors is oregano oil. Unlike many conventional antibiotics, oregano oil does not kill good bacteria, but rather selectively targets harmful bacteria and fungus [86]. This is due to its complex mixture of metabolites, which include carvacrol, thymol, rosmarinic acid and many more. These metabolites have been shown to have potent antimicrobial activity against bacteria and fungi by disrupting the cell membranes, inhibiting growth, and causing cellular damage.

Berberine and garlic are two other powerful allies in fighting SIBO, SIFO and biofilms. Berberine has been shown to have strong antibacterial, antifungal, and antiprotozoal effects, making it effective against a wide range of pathogens. Garlic contains allicin, which has been shown to have strong antibacterial and antifungal effects, making it a potent biofilm disruptor [81].

When using biofilm disruptors, it is important to note that patients may experience a die-off effect, also known as the Herxheimer reaction. This occurs when large numbers of pathogens are killed off, causing the release of toxins that can cause temporary symptoms such as headaches, fatigue, and gastrointestinal distress. To minimize this effect, it is recommended to start with a low dosage and gradually increase it as the patient tolerates it [81].

In addition to biofilm disruptors, the use of activated charcoal has been found to be beneficial as it acts as a barrier to reduce the excessive absorption of toxins. Prokinetic medications may also be indicated to allow for adequate peristaltism and elimination of toxins via the digestive route.

In such cases, the use of herbal antimicrobials that disrupt biofilms have been found to be beneficial in refractory patients receiving only HDVD + AID. The presence of LPS, mycotoxins, inflammatory markers, and antibody titers tend to decrease and even normalize once the underlying infection has been eliminated. **In our clinical practice we have noticed that vitamin D (HDVD) requirements also tend to be less when the infection (dysbiosis) has been treated.**

Finally, HDVD therapy combined with an anti-inflammatory diet can be an effective treatment for autoimmune diseases. However, it is important to ensure that patients receive all the necessary cofactors to support vitamin D metabolism and maintain gut integrity. In some cases, addressing underlying infections may also be necessary for optimal results.

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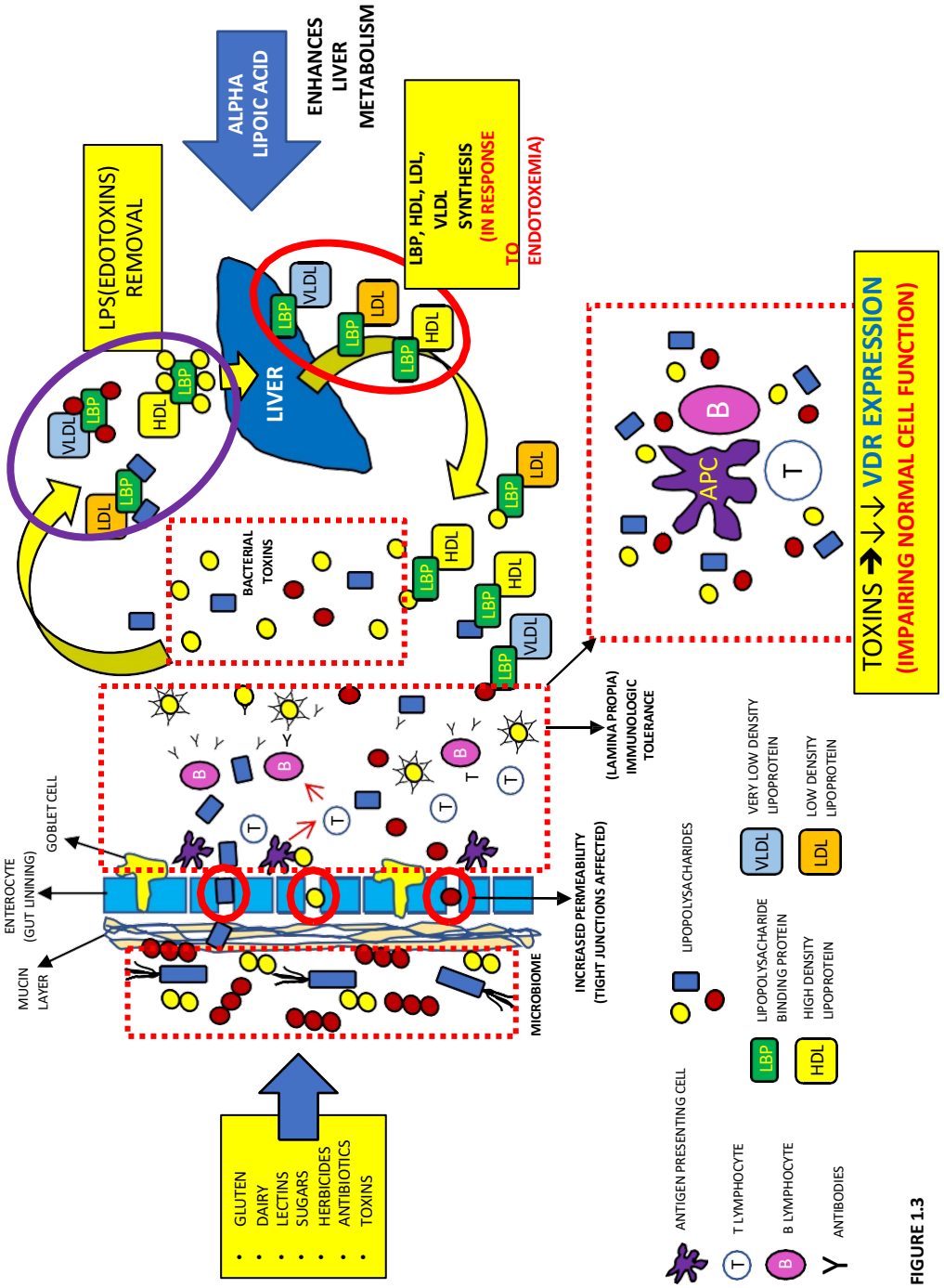
ALPHA LIPOIC ACID
ENHANCES LIVER METABOLISM
LPS(EDOTOXINS) REMOVAL
LBP, HDL, LDL, VLDL SYNTHESIS (IN RESPONSE TO ENDOTOXEMIA)
LIVER
BACTERIAL TOXINS
APC
TOXINS ➔↓↓ VDR EXPRESSION (IMPAIRING NORMAL CELL FUNCTION)
ENTEROCYTE (GUT LINING)
GOBLET CELL
MUCIN LAYER
MICROBIOME
INCREASED PERMEABILITY (TIGHT JUNCTIONS AFFECTED)
(LAMINA PROPIA) IMMUNOLOGIC TOLERANCE
GLUTEN
DAIRY
LECTINS
SUGARS
HERBICIDES
ANTIBIOTICS
TOXINS
LIPOPOLYSACCHARIDES
VERY LOW DENSITY LIPOPROTEIN
LOW DENSITY LIPOPROTEIN
LIPOPOLYSACCHARIDE BINDING PROTEIN
HIGH DENSITY LIPOPROTEIN
ANTIGEN PRESENTING CELL
T LYMPHOCYTE
B LYMPHOCYTE
ANTIBODIES

FIGURE 1.3

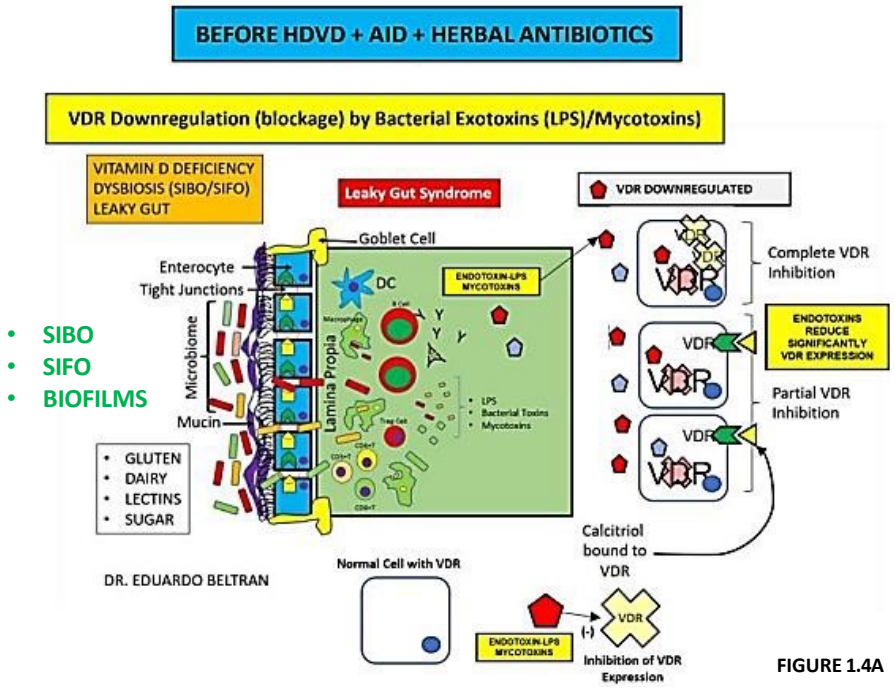

FIGURE 1.4A

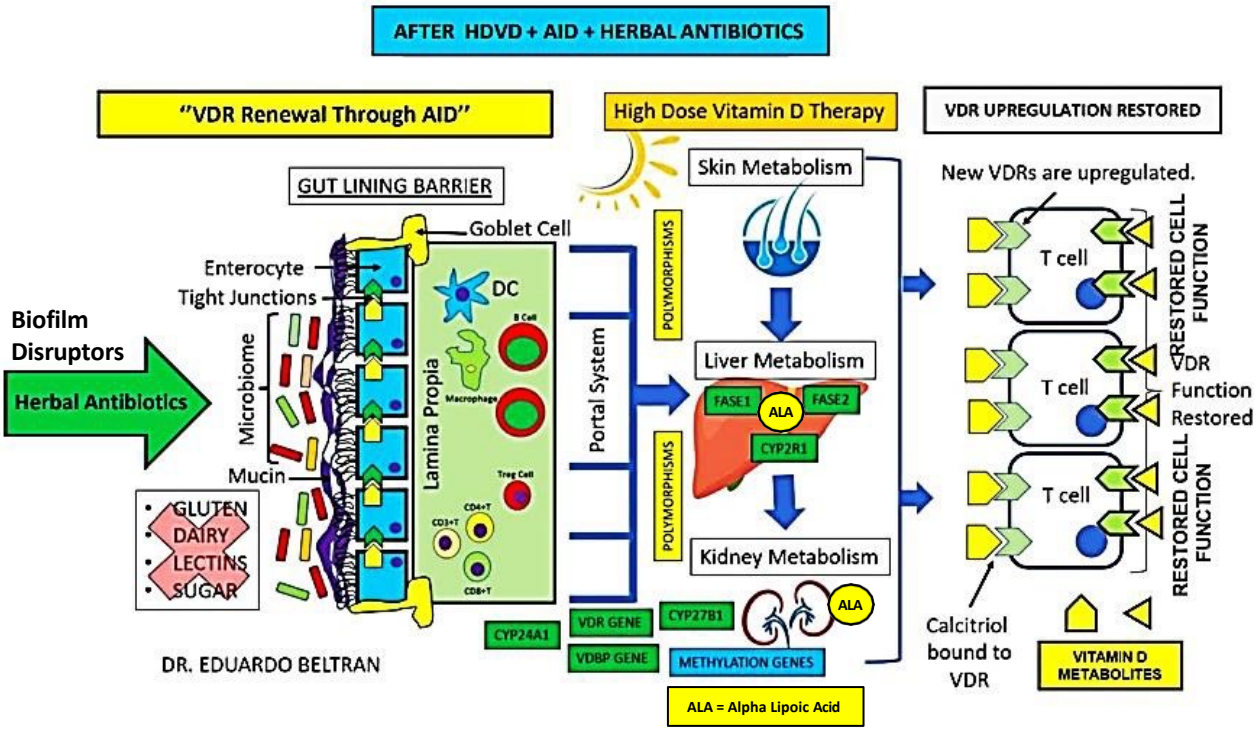

FIGURE 1.4B

CONCLUSIONS

The link between gut dysbiosis and vitamin D resistance is an important one that is often overlooked in mainstream medicine. However, it is becoming increasingly clear that chronic infections such as SIBO, SIFO, and resistant biofilms can interfere with the expression of vitamin D receptors (VDRs) in our bodies, leading to reduced VDR metabolite affinity and impaired cellular response to circulating vitamin D metabolites.

When these infections are eliminated through the use of herbal antimicrobials and anti-inflammatory diets, the upregulation of VDR expression can occur. This upregulation can allow for better VDR metabolite affinity and, in turn, better cellular response to circulating vitamin D metabolites. This is especially important for immune cells, which play a crucial role in protecting our bodies against pathogens and maintaining overall health.

The concept of **VDR Renewal through anti-inflammatory diet**, described by E. Beltran, highlights the importance of addressing chronic infections and gut dysbiosis in the management of autoimmune conditions. By recognizing the role of infections in vitamin D resistance, healthcare providers can better understand the underlying mechanisms of autoimmune diseases and develop more effective treatment plans that target the root cause of the problem by introducing use of herbal antimicrobials when needed.

Incorporating the concept of VDR Renewal into mainstream medicine may require a shift in the way we approach autoimmune diseases. Rather than simply treating symptoms. Healthcare providers may need to consider a more holistic approach that addresses gut health and chronic infections in order to improve VDR expression and enhance the overall function of our immune system.

SCAN ME

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