ABSTRACT
Vitamin D, which is also known as "sunshine vitamin," plays a pivotal role in both bones as well as non-bone organs. The ubiquitous expression of VDR in numerous tissues, including the kidney, heart, muscle, breast, colon, prostate, brain and immune cells, makes this as a natural target of modulation in disease pathogenesis including variety of cancers, metabolic syndrome, renal transplant and dermal disorders. Low vitamin D levels have become an epidemic across the continent irrespective of amount of sunshine during different seasons. The epidemiological studies estimate that currently at least 1 billion people suffer from low vitamin D levels. Vitamin D receptors regulate a number of signaling pathways. These pathways are often involved in inflammation and tumor growth and especially in the epithelial cells of the skin, breast, prostate and colon in case of cancer. Vitamin D plays important roles in calcium homeostasis, cell proliferation and cell differentiation to many target tissues, which is considered to be mediated through the nuclear VDR control of target genes. Vitamin D dysfunction may be in part inherited as suggested by previous research and VDR polymorphisms is perceived to be the primary reasons of this inherited dysfunction of VDR. This review discusses studies highlighting the role of vitamin D with more emphasis in metabolic syndrome, diabetes, breast, ovarian and prostate cancer, psoriasis, and allograft outcomes other than vitamin D's traditional role related to bone health.

INTRODUCTION
Vitamin D, which is also known as "sunshine vitamin," plays a pivotal role in both bones as well as non-bone organs. The paracrine and autocrine biological activities of vitamin D are exerted by binding to its intracellular receptor known as vitamin D receptor (VDR). The ubiquitous expression of VDR in numerous tissues, including the kidney, heart, muscle, breast, colon, prostate, brain and immune cells, makes this as a natural target of modulation in disease pathogenesis including variety of cancers, metabolic syndrome, renal transplant and dermal disorders [Table 1]. The underlying mechanisms of VDR-mediated protective roles can be explained in two broad categories, namely cell proliferation and immunological pathways. Increased cell proliferation and differentiation through dysregulation of VDR functions lead to cancerous conditions. Similarly, lack of control in VDR-mediated regulated immunological pathways is responsible for dermal disorders; immunodeficiency conditions and transplants related complications.

Low vitamin D levels have become an epidemic across the continent irrespective of amount of sunshine during different seasons. The epidemiological studies estimate that currently at least 1 billion people suffer from low vitamin D levels. In spite of our ability to synthesize vitamin D3, majority of the population requires additional amounts through our diet or health supplements to maintain the optimum levels that are relevant to chemopreventive or therapeutic in nature. Vitamin D3 is physiologically converted into its active form called 1α,25-dihydroxyvitamin D3 [1α,25(OH)2.D3 or calcitriol] which is responsible for binding to VDR and exerting its critical functions. Because vitamin D is not active in its native form and a specific receptor is present for its functions, it is also referred as a prohormone rather than a vitamin.

Vitamin D receptor (VDR) components and their functions
Three distinct regions which include an N-terminal dual zinc finger DNA binding domain, a C-terminal ligand-binding activity domain and an unstructured region that links the two functional domains of this protein together constitutes the VDR protein. The C-terminal region of the molecule is the most complex and is comprised of 12 α-helices. Amino acid contacts within a subset of these α-helices form a dynamic ligand-binding pocket. Two independent protein interaction surfaces on the VDR protein are formed as a result of active vitamin D’s selective binding. These two independent protein interaction surfaces facilitates interaction with a heterodimer partner required for specific DNA binding and the recruitment of large co-regulatory complexes required for gene modulation.

VDR can also be post-transnationally modified through phosphorylation thereby modulating and fine-tuning its transcriptional activity. These domains within the VDR create a macromolecule receptive to physiologically relevant levels of circulating active vitamin D. This further directs cellular regulatory mechanism to specific subsets of genes whose protein products are key to vitamin D response [Figure 1]. Vitamin D receptors regulate a number of signaling pathways. These pathways are often involved in inflammation and tumor growth and especially in the epithelial cells of the skin, breast, prostate and colon in case of cancer. Vitamin D plays important roles in calcium homeostasis, cell proliferation and cell differentiation to many target tissues, which is considered to be modulated through the nuclear VDR control of target genes. Intracellular VDR, which mediates changes in gene expression, is responsible for various biological actions of active vitamin D. Binding of receptor’s to regulatory regions of target genes

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: invoice@jbclinpharm.org

Table 1: VDR gene polymorphism and its impact on disease conditions

<table>
<thead>
<tr>
<th>Polymorphism (SNP)</th>
<th>Disease Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>FokI rs2228570</td>
<td>Metabolic syndrome, Obesity, diabetes, Breast cancer</td>
</tr>
<tr>
<td>ApaI rs7975232</td>
<td>Diabetes, Psoriasis, Ovarian cancer</td>
</tr>
<tr>
<td>TaqI rs731236</td>
<td>Metabolic syndrome, Obesity, breast cancer, new onset diabetes at transplant,</td>
</tr>
<tr>
<td>BsmI rs1544410</td>
<td>Metabolic syndrome, Obesity, Breast cancer, BPH, Prostate cancer, allograft survival in renal transplant</td>
</tr>
</tbody>
</table>

SNP- Single nucleotide protein; BPH-Benign Prostatic Hyperplasia

Figure 1: Vitamin D function cascade and implications of vitamin D receptor gene polymorphism on diseases pathogenesis. RXR- Retinoid X Receptor; VDRE- Vitamin D Responsive Elements
is prompted by the activation of the VDR through direct interaction with active vitamin D (this further leads to the formation of large protein complexes). Biological reactions in most target cells are triggered by the expression of networks of target genes. These reactions sometimes are tissue specific or highly complex performing homeostatic control of mineral metabolism to that of controlling the growth, differentiation and functional activity of numerous cell types including the immune system, skin, the pancreas and bone, where the genes targets are numerous. Vitamin D and the cytokine gamma interferon (IFN-γ) are the activators of macrophage immune function. IFN-γ induces vitamin D synthesis by macrophages and inhibits vitamin D induction of 24-hydroxylase, a key enzyme in vitamin D inactivation, causing high levels of vitamin D in serum leading to hypercalcemia in conditions such as sarcoidosis, tuberculosis, and several granulomatoses. Excessive vitamin D which results into hypercalcemia has also receiving much attention from the renal transplant community, since it has been associated with the negative impact on both the graft and patient outcomes in renal transplant recipients. On the other hand IFN-γ, which induces vitamin D synthesis, its polymorphisms have been associated with BK virus nephropathy and cytomegalovirus infection.

Role and impact of vitamin D receptor gene polymorphism

As stated earlier, at least half of adults in developed countries lacks adequate levels of vitamin D. Vitamin D dysfunction may be in part inherited as suggested by previous research and VDR polymorphisms is perceived to be the primary reasons of this inherited dysfunction of VDR. The involvement of vitamin D in the development of metabolic syndrome has been explored in one study. Metabolic syndrome is a cluster of conditions such as high blood pressure, high blood sugar, excess body fat around the waist, and abnormal cholesterol or triglyceride levels that occur together thereby increasing the risk of developing cardiovascular disease and type 2 diabetes mellitus (T2DM). Although, the role of vitamin D in metabolic syndrome remains to be completely explained, it was suggested that the active vitamin D may be responsible for reduced insulin secretion and sensitivity, obesity, diabetes and hypertension. Low conc. of active vitamin D also been suggested to play role in the development and progression of non-alcoholic fatty liver disease, which is an independent component of metabolic syndrome. Several polymorphisms such as ApaI (VDR 7975232 C>T), BsmI (VDR 1544410 A>G), FokI (VDR 2228570 C>T), and TaqI (VDR 731236 T>C) have been reported for the VDR gene. Some of these polymorphisms are reported to be associated with type II diabetes mellitus, insulin secretion and metabolic changes related to obesity. It has been suggested that a length of the VDR, affected by the presence of the polymorphisms, could lead a lower activation of target cells, since a longer VDR protein appears to have a decreased transcriptional activity. In this study conducted in Brazil, the association of components of metabolic syndrome was investigated with the presence of polymorphisms in VDR gene [VDR 1544410 A>G (BsmI); VDR 2228570 C>T (FokI); and TaqI (VDR 731236 T>C)] have been reported for the VDR gene. In this study, influence of VDR gene polymorphisms on susceptibility to type I diabetes, and rates of glutamic acid decarboxylase (GAD65) autoantibody and islet cell autoantibody (ICA512) were studied in 157 type I diabetic patients and 248 unrelated normal controls. The allele frequency of the BsmI and Apal polymorphisms, but not TaqI polymorphism, differed between patients and controls. However, after correction for the three different polymorphisms tested, only the BsmI was found significantly associated with type I diabetes.

The association of polymorphisms in the VDR gene including rs10735810 (FokI), rs11568820 (Cdx-2), rs1544410 (BsmI), rs7975232 (Apal), rs731236 (TaqI), and BsmI-Apal-TaqI combined genotypes with ovarian cancer risk was examined among 313 women with epithelial ovarian carcinoma and 574 controls in a study by Lurie and colleagues. The associations of VDR polymorphisms with risk were found generally inconsistent across the ethnic groups. Heterozygous and homozygous Apal A allele carriers were at increased ovarian carcinoma risk compared with homozygous carriers of the Apal A allele among Caucasian women. Whereas, Caucasian heterozygous carriers of FokI A allele were also at increased risk of ovarian carcinoma compared with homozygous carriers of the common allele. Ovarian cancer risk was found significantly decreased among Cdx-2 A allele heterozygotes compared with homozygote G allele carriers among Japanese women.

In a population based case control study conducted among Hispanic, African-American, and non-Hispanic White women aged 35-79 years from the San Francisco Bay Area of California in 1993 to 2003, possible associations of breast cancer with sun exposure, the principal source of vitamin D, and VDR gene polymorphisms (FokI, TaqI, BglII) were examined. A total of 1,788 newly diagnosed cases and 2,129 controls were interviewed in person and measurements on skin pigmentation were taken on the upper arm (a sun-protected site that measures constitutive pigmentation) and on the forehead (a sun-exposed site) using reflectometry. A high sun exposure index based on reflectometry was associated with reduced risk of advanced breast cancer among women with light constitutive skin pigmentation. This study supported the hypothesis that sunlight exposure reduces the risk of advanced breast cancer among women with light skin pigmentation.

In another study, polymorphisms in the 5’ and 3’ ends of the VDR gene were explored for their influence on breast cancer risk among 143
Latina women with breast cancer and 300 cohort controls. Both the BsmI and poly-A polymorphisms in the 3' end of the VDR gene were associated with breast cancer risk, with a trend for increasing risk with increasing number of BsmI B alleles or short (S) poly-A alleles. These results suggested that polymorphic variation in or near the 3' end of the VDR gene influences breast cancer risk in Latina women. A polyploidy with this gene, could predispose patients to the development of breast cancer or allograft survival in renal transplant,[31] however, the molecular biology and transgenic animal work is scarce to affirm this finding from the clinical or epidemiological population studies. A well-designed validation study for each of the major polymorphic VDR SNPs will establish the pathophysiological significance of each of these polymorphic forms. The abundance data across the ethnicity is another facet of VDR polymorphism area. It is a well-known fact in the pharmacogenomics domain that frequency of different genotypes is not consistent across the population; however, it is critical that we identify the potential target population for VDR polymorphism in a systematic way. Although there is strong likelihood regarding the involvement the VDR gene polymorphic forms in multiple disease conditions, there need to be validated data for any intervention related to that aberration.

Because of the abundance of VDR in the population, it is imperative that, aside from measuring vitamin D plasma levels, identification of VDR genotype at the point-of-care is implemented to understand the vitamin D function status in an individual. In general, vitamin D follows a U-shape dose-response curve, which means at higher concentrations (>100 ng/ml or more) the person may experience vitamin D toxicities such as kidney stone.[32] Knowledge of VDR functional status will ensure unnecessary supplementation of vitamin D3 at supraphysiologic doses. Combining the VDR genotype and vitamin D level information will facilitate the understanding of the root cause of vitamin D deficiency effects in an individual. Other confounding factors such as concomitant intake of modulators of wild type and polymorphic VDR protein also need to be considered.

CONCLUSIONS

Genetic studies combined with epidemiological data and can provide excellent opportunities to link molecular insights to reveal modest and subtle but true biological effects. To explain variation of risk in common diseases, abundance of polymorphisms in the human genome as well as their high frequencies in human populations made it possible to predict such risk. Polymorphisms in the VDR gene have been linked to several diseases, including osteoporosis, diabetes, cancer and cardiovascular disease etc. Polymorphisms are usually suspected of having only modest and subtle effects, however, recent studies have indicated otherwise. Even though, many VDR gene polymorphisms exist, their influences on VDR protein function are largely unknown. Eventually, results of such type of research will deepen our understanding of variability in the encoding genes of Vitamin D. This could further find applications in risk-assessment of disease and in predicting response to the treatment. Our review has summarized the vast amount of information regarding VDR polymorphisms and its links to various disease conditions and discussed its possible role as diagnostic tool or predictive marker in the future.

REFERENCES

Vitamin D Receptor (VDR) Gene Polymorphism: Implications on Non-Bone Diseases

Sakharkar P, et al.: Vitamin D Receptor (VDR) Gene Polymorphism: Implications on Non-Bone Diseases


