A Review on Relationship of SNP at rs7975232 (*Apa*I) of VDR Gene And Different Diseases in Different Population

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.)

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Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The thesis titled "A Review on Relationship of SNP at rs7975232 of VDR Gene and Different Diseases in Different Populations" submitted by Sharif Ahamed (19146037), of Summer 2023 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

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Ethics Statement

This study did not involve any human participants, human specimens or tissue, vertebrate animals or cephalopods, vertebrate embryos or tissues and field research.

Abstract

A variety of health conditions arise from changes in the gene responsible for the vitamin D receptor (VDR). This gene provides instructions for making a protein called the vitamin D receptor, which is important for how vitamin D works in the body. The way these molecules interact has important implications for predicting a range of health conditions. It's believed that the start of many health problems is connected to differences in the VDR gene. Researchers are particularly interested in studying the effects of these gene differences on various health conditions like osteoporosis, periodontist, hepatitis C, breast cancer, and childhood asthma. Additionally, a lot of research has shown that vitamin D also has a role in how our immune system functions better. This means that differences in the VDR gene could possibly be linked to the development of the health issues mentioned earlier. This study suggests that a specific type of genetic modification, called a single nucleotide polymorphism (SNP) at rs7975232 found the VDR gene, is connected to various health problems.

Keywords: VDR gene, Vitamin D receptor, Single nucleotide polymorphism, Osteoporosis, Periodontist, Hepatitis C, Breast Cancer, and Childhood Asthma

Dedication

I dedicate this thesis to my parents and my mentor Dr. Aminul Haque. Their support and guidance have not just been invaluable to my academic journey but also my personal life, and I am truly grateful for their presence in my life.

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List of Acronyms

LD	Linkage Disequilibrium
BMD	Bone Mineral Density
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
NAFLD	Non-Alcoholic Fatty Liver Disease
HCC	Hepatocellular Carcinoma
IαI	Inter Alpha Inhibitor
VDR	Vitamin D Receptor
SNP	Single Nucleotide Polymorphisms
RFLP	Restriction Fragment Length Polymorphism

Chapter 1

Introduction

1.1 Background

The Vitamin D Receptor (VDR) gene is accountable for encoding a vital protein integral to the preservation of strong skeletal structure, dental health, and immunoregulation. This genetic locus specifically codes the synthesis of the VDR receptor protein, strategically positioned on the cell surface of diverse tissues, including the bones, skin, and immune system. Unfortunately, specific allelic variations within the VDR gene, denoted as polymorphisms, have been identified as precursors to a spectrum of disease. These polymorphic sequences engender a diverse spectrum of effects upon both the functional capacity of the gene and the protein it produces.

Noteworthy disease associated with VDR polymorphisms are rheumatoid arthritis, breast cancer, Parkinson's disease, and osteoporosis. As the inquiry into etiology and management of these disease has unfolded, it has become evident that vitamin D endows vital anti-inflammatory properties. Additionally, vitamin D exhibits potential as a formidable mediator in the regulation of calcium homeostasis, thereby amplifying its immunomodulatory effects. Consequently, an imperative has arisen to acquire an in-depth comprehension of how the body regulates vitamin D.

This review aims to find out the correlation between vitamin D and various diseases, with a particular emphasis on a discrete nucleotide polymorphism situated at the *ApaI* locus of the VDR gene. The purview of this inquiry extends to an exploration of the VDR polymorphism at both allelic and genotypic levels to better comprehend this association and contribute to the overall understanding of these diseases for the purpose of this review.

1.2 Single Nucleotide Polymorphism in VDR gene

Single nucleotide polymorphisms (SNPs) are instances of genetic variation characterized by the alteration of a single nucleotide within the DNA sequence. These modifications predominantly involve the nucleotides adenine, guanine, thymine, and cytosine. The presence of such alterations within the genetic framework of the Vitamin D Receptor (VDR) gene has led to the revelation of a diverse spectrum of disorders correlated with these polymorphisms. Notably, polymorphic variances in the VDR gene have been implicated in an array of conditions, including but not restricted to rheumatoid arthritis (Puncevičienė et al., 2021). The VDR gene assumes a pivotal role in orchestrating the assimilation of vitamin D within the human physiological milieu. This occurs through the formation of a molecular alliance between vitamin D and the VDR receptor, thereby facilitating intended physiological consequences (Mukhtar et al., 2019).

As a consequence, it follows that single nucleotide polymorphisms manifesting within the genetic architecture of the VDR gene exert an intricate influence on the body's responsiveness to supplemental vitamin D. This, in turn, establishes a complex interplay between these SNPs and a diverse array of disorders, encompassing conditions such as osteoporosis, autoimmune maladies, neoplastic disorders, and cardiovascular pathologies. The comprehensive engagement of the VDR gene across a spectrum of disorders is inherently rooted in the existence of multiple polymorphic loci. Functioning as a ligand-dependent transcriptional modulator, VDR forms an intricate molecular complex with hormonally active vitamin D, thereby intricately overseeing the expression of genes orchestrating inflammatory responses and immune modulation (Nagpal et al., 2005). Remarkably, this molecular complex finds manifestation across a broad spectrum of cell types, including immune cells, neural cells, and glial cells (Kongsbak et al., 2013) (Wang et al., 2005).

Among the polymorphic loci that have undergone extensive investigation within the realm of the VDR gene, noteworthy instances include *BsmI, ApaI, TaqI*, and *FokI* (Norman, 2008). These polymorphisms are strategically positioned within the genetic makeup of the VDR gene, with *BsmI* and *ApaI* localized within intron 8 and *TaqI* occupying a site within exon 9 (Uitterlinden et al., 2002). On the other hand, the *FokI* polymorphism resides within exon 2, thereby resulting in distinct protein isoforms characterized by variations in length. Specifically, the truncated variant of the protein (composed of 424 amino acids) showcases enhanced activity relative to its elongated counterpart (comprising 427 amino acids). It is pertinent to note that autonomous investigations have underscored a direct nexus between the *FokI* genetic variant and an elevated susceptibility to rheumatoid arthritis and multiple sclerosis. Furthermore, a plenitude of empirical studies has underscored the potential ramifications of this SNP on the immune responsiveness of the organism (Singh et al., 2018). Notably, *ApaI* has also emerged as an SNP associated with sclerosis.

1.3 Disease associated with VDR gene polymorphism

1.3.1 Breast Cancer:

Globally, breast cancer assumes a prominent role as a leading cause of mortality among women. It constitutes 16% of all female malignancies and 22% of invasive female neoplasms. Within the context of Iranian women, breast cancer has emerged as the most prevalent form. The influence of genetic variations on growth, differentiation, and apoptosis mechanisms possesses the capacity to modulate an individual's susceptibility to breast cancer (Vogelstein & Kinzler., 2004). While a definitive gene responsible for hereditary breast cancer remains unidentified, mutations in specific suppressor genes, notably BRCA1, ATM, TP53, PALB2, RAD50, and MLH, are observed in roughly fifty percent of familial breast cancer cases.

Numerous investigations have underscored the substantial role of vitamin D in mitigating diverse cancer types, including breast cancer. The Vitamin D Receptor (VDR), typically expressed in the mammary gland, functions to counterbalance estrogen-induced proliferation, facilitate differentiation, and potentially contribute to the adversarial control of mammary epithelial cell proliferation. Given the potential influence of VDR gene variations on receptor function, the scrutiny of single nucleotide polymorphisms (SNPs) within the VDR gene assumes a pivotal significance. In this vein, it can be deduced that VDR polymorphisms wield the potential to impact vitamin D metabolism and levels of 25-hydroxyvitamin D (25(OH)D) (Tiosano et al., 2001).

1.3.2 Periodontitis:

Periodontitis refers to an infection that affects the supportive tissues encircling the teeth. This oral malady manifests in either a persistent or an aggressive manner, as substantiated by earlier investigations (Tiosano et al., 2001). It significantly impacts a considerable segment of the populace (Albandar et al., 1999). Chronic periodontitis is prevalent, impacting approximately 30% of adults, while severe and destructive forms of periodontal disease materialize in about 7-13% of the adult population. Aggressive periodontitis, formerly known as early onset periodontitis, appears to be less widespread. Because of its persistent nature, periodontitis is postulated to originate from an intricate interplay of causative factors, encompassing intricate interactions involving microbiological, genetic, and environmental constituents, all of which collectively determine the inception and progression of the ailment (Mashhadiabbas et al., 2018).

The vitamin D receptor (VDR) gene has emerged as a potential genetic susceptibility factor, delineated by a distinct restriction fragment length polymorphism (RFLP), implicated across diverse populations in various infections and ailments, including periodontitis (Brett et al., 2005). A conspicuous hallmark of periodontal diseases is the diminishment of alveolar bone. An array of scientific inquiries has unveiled the existence of gene polymorphisms capable of influencing bone mineral density (BMD), bone turnover, and bone loss, particularly in the context of osteoporosis. Significantly, specific VDR gene polymorphisms have exhibited robust associations with BMD in select research investigations (Thakkinstian et al., 2004). Vitamin D's impact on the progression of periodontal disease is underscored by dual mechanisms: its modulatory effects on the immune system and its influence on BMD (Krall et al., 2001). Within diverse biological processes, the VDR emerges as a pivotal participant, including the regulation of bone metabolism, modulation of immune responses, and orchestration of cellular proliferation and differentiation (Uitterlinden et al., 2004).

Nonetheless, the association between VDR polymorphisms and the propensity for chronic and aggressive periodontal disease has yielded incongruous outcomes across diverse association studies.

1.3.3 Liver cirrhosis:

The Hepatitis C virus (HCV) presents a substantial global health predicament, with an estimated 71 million individuals believed to harbor chronic infections (Blach et al., 2017). Persistent HCV infection is intricately associated with notable complications, notably hepatic fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) (Hajarizadeh et al., 2013). HCC ranks as the sixth most prevalent malignancy across the globe, representing a significant portion of primary liver cancer incidences (75 to 85%), and ranking fourth in the hierarchy of cancer-related mortalities (Bray et al., 2018).

In conjunction with HCV, an array of other risk elements has been intertwined with the genesis of HCC, encompassing chronic HBV infection, non-viral cirrhosis, alcohol consumption, non-alcoholic fatty liver disease (NAFLD), exposure to aflatoxin, Wilson's disease, hemochromatosis, familial history or genetic predisposition, and tobacco use (Tang et al., 2018).

While the correlation between HCV and HCC is solidly grounded, the precise intricacies driving carcinogenesis, which encompass both host and viral constituents, remain partially unveiled (Hung et al., 2014). Numerous genetic components, particularly gene polymorphisms governing inflammatory cytokines, have been pinpointed as conceivable agents in HCC onset among individuals afflicted with chronic HCV infection (Bataller et al., 2003).

1.3.4 Childhood Asthma:

Asthma, a prevailing and chronic respiratory ailment in children, is characterized by airway inflammation and hyper-responsiveness, as delineated by (Page et al., 2013). It materializes through intermittent episodes marked by breathlessness, wheezing, and coughing. Over the course of the last decade, a discernible upsurge in the prevalence of childhood asthma has been observed, as documented by (Lin et al., 2014). Specifically, within the United States, an estimated 7.1 million children grapple with this condition, as underscored by (Howland et al., 1988). Alarmingly, asthma-related complications in early life exact a formidable toll, contributing to an annual toll of no less than 250 thousand lives, according to (Bousquet et al., 2010).

Extensive inquiry has been directed towards discerning potential risk factors, including early-life exposure to ambient air pollution, as illuminated by (Q. Deng et al., 2015), as well as microbial and metabolic perturbations during infancy, as explored by (Arrieta et al., 2015), among other contributing elements. Furthermore, an emerging body of evidence intimates that the genetic landscape, featuring pivotal genes such as interleukin-17, interleukin-27, and the vitamin D receptor (VDR) gene, assumes a pronounced role in dictating susceptibility to asthma, as expounded upon by (Du et al., 2016).

1.3.5 Osteoporosis:

Osteoporosis represents a widespread pathological state characterized by diminished bone mineral density, altered microarchitecture of bone tissue, and an augmented susceptibility to fractures. The diagnostic criteria for osteoporosis are predicated upon assessments of bone mineral density (BMD) at anatomical sites such as the spine or hip, wherein BMD values falling

2.5 standard deviations (SD; T-score values) or more below the mean of young adults, as stipulated by (Kanis et al., 1994), serve as the demarcating threshold.

The zenith of peak bone mass is reached during early adulthood, followed by a gradual diminution in postmenopausal women due to the waning production of estrogen, which intricately influences bone homeostasis alongside modulating calcium absorption within the gastrointestinal milieu and renal function. Antecedent studies rooted in twin and familial frameworks have underscored the substantive contribution of genetic determinants in shaping bone mineral density. Twin-based investigations have estimated the heritability of BMD within a range of 50% to 85%, with the preponderance of prominent effects localized to the axial skeletal domain (Slemenda et al., 1991). Furthermore, empirical evidence has substantiated that genetic factors confer between 27% to 68% of the variance in osteoporotic fracture susceptibility (Michaëlsson et al., 2005).

Osteoporosis constitutes a complex polygenic trait influenced by an intricate interplay of multiple genes, each orchestrating subtle modulations in bone mass and assorted parameters that collectively contribute to the propensity for fracture. Polymorphic variants manifesting within several candidate genes, which are closely tied to bone mass or vulnerability to osteoporotic fractures, have been delineated through expansive population-based inquiries and meticulous case-control analyses. Among these genes, the vitamin D receptor (VDR), collagen type IαI gene, and estrogen receptor stand as prominent exemplars.

1.3 Objective

This review article focuses on the investigation of single nucleotide polymorphisms within the *ApaI* gene and their intricate connections with various diseases, namely breast cancer, periodontitis, liver cirrhosis, childhood asthma, and osteoporosis. The fundamental objectives of this comprehensive review encompass the provision of contemporary insights to researchers, clinicians, and patients alike. The aim is to furnish an all-encompassing and current portrayal of the diseases linked with the VDR ApaI polymorphism, while simultaneously underscoring the paramount importance of ongoing research endeavors in augmenting our comprehension of these incapacitating ailments and our therapeutic capabilities to address them.

Chapter 2

Methods

This paper focuses on reviewing the relationship between a specific single nucleotide polymorphism (SNP) called *ApaI* (rs7975232) and its association with various diseases. The author conducted a literature search using specific keywords such as "Vitamin D," "VDR" (Vitamin D receptor), "VDR polymorphism," "Osteoporosis," "Breast Cancer," "*Apa*I," "rs7975232," "Periodontitis," "Asthma," and "liver cirrhosis" in databases including PubMed, Medline, Science Direct, Nature, and Google Scholar. These databases were chosen to ensure the authenticity of the articles used as sources for information and data collection in this review paper.

In cases where the full text of an article was not accessible, the author requested a reprint from the corresponding author. Only articles with complete texts were considered for data retrieval. The publications of interest covered different ethnicities, and DNA and allele information was given priority. Once these criteria were met, the author thoroughly read all the articles to identify the connection between the VDR SNP and its impact on patients with various diseases. Specifically, the focus was on the *ApaI* (rs7975232) polymorphism, and the author selectively examined the results pertaining to this SNP in their article.

By studying multiple articles and extracting data from 25 relevant sources, it was concluded that VDR polymorphism is associated with certain diseases due to differences in allele and genotype distribution. The author aimed to summarize the findings in a simplified manner to enhance readers' understanding. Each study's data, including the author's name, year of the study, ethnicity of the subjects, genotype distribution, allele distribution, and other relevant information, were calculated and analyzed

Chapter 3

Discussion

3.1 Association with Breast Cancer

A study conducted by (El-Shorbagy et al., 2017) revealed that the *ApaI* polymorphism in the VDR gene served as a genetic risk factor for breast cancer among the Egyptian female population. In a similar vein, the *TaqI* polymorphism was investigated by (Ahmed et al., 2019) who found no apparent association between this genetic variant and breast cancer risk. Interestingly, (El-Shorbagy et al., 2017) did find evidence of an association between this polymorphism and an elevated risk of breast cancer. The disparate outcomes across these studies underscore the potential influence of various factors, such as race, diet, lifestyle, and environmental elements, on the complex relationship between VDR gene polymorphisms and breast cancer risk.

Recent research has delved into exploring the link between VDR gene polymorphisms and the risk of breast cancer, producing diverse findings. As an illustration, a study conducted by (Ahmed et al., 2019), focusing on the Ethiopian female population revealed that the ApaI polymorphism did not manifest any connection with breast cancer across various genetic models. However, upon closer examination, the CC genotype demonstrated an association with elevated levels of 25 (OH) D3 in plasma within the tamoxifen receiving group

3.2 Association with Periodontitis

Conducting a comprehensive database search, (H. Deng et al., 2011) incorporated 15 distinct studies involving 1338 cases and 1302 controls. Among these, chronic periodontitis cases, particularly within Asian populations, exhibited a significantly higher frequency of the AA

genotype of the *ApaI* polymorphism. This finding raises the possibility of a link between this genetic variant and the prevalence of chronic periodontitis. Furthermore, (Galal et al., 2021) uncovered additional support for this concept by demonstrating that a VDR haplotype formed through the combination of *ApaI* polymorphisms was associated with an elevated risk of severe chronic periodontitis, particularly among Japanese men.

In a separate investigation by (H. Deng et al., 2011), individuals afflicted with chronic periodontitis demonstrated a notable decrease in the occurrence of the bb genotype of *BsmI*, accompanied by an elevated prevalence of the AA genotype of *ApaI* and the TT genotype of *TaqI* among the Asian cohort. Employing the Bonferroni correction method, it was established that even after accounting for multiple statistical comparisons, a substantially higher frequency of the AA genotype of *ApaI* was observed among individuals with chronic periodontitis within the Asian population. No substantial variation was observed across any genotype of *FokI* among the participants of the study.

3.3 Association with Liver cirrhosis

In a separate investigation, (Naito et al., 2007) conducted a study involving 76 patients with HCV-related liver cirrhosis. Among these patients, 48 had hepatocellular carcinoma (HCC) in addition to cirrhosis, while the remaining 28 had liver cirrhosis only. Through comprehensive assessments, including medical history, clinical examination, laboratory investigations, abdominal ultrasonography, and genotyping of the VDR gene has a significantly higher frequency of the *ApaI* CC genotype in HCC patients compared to those without HCC. While no statistically significant differences were found regarding *TaqI* genotypes, the presence of the *ApaI* CC genotype was notably associated with the severity of liver disease in both patient

groups. Moreover, the carriage of the *ApaI* CC genotype emerged as an independent predictor for HCC in individuals with HCV-related liver cirrhosis.

Similarly, (H. Deng et al., 2011) conducted another study which highlighted a significant prevalence of the VDR ApaI CC genotype among patients with cirrhosis who also presented hepatocellular carcinoma (HCC), as opposed to cirrhotic patients without HCC. These findings are consistent with earlier research reporting similar outcomes. Interestingly, some studies, including the present one, did not uncover a substantial correlation between HCC and the TaqI polymorphism. Furthermore, the potential implications of VDR ApaI and TaqI polymorphisms on the severity of liver disease in individuals with both liver cirrhosis and HCC were explored by the researchers. It was observed that individuals harboring the ApaI CC genotype exhibited more severe liver disease, as indicated by Child C classification and a higher MELD score, compared to those with the ApaI CA/AA genotypes. However, the presence of diverse TaqI genotypes did not reveal any significant correlation with the severity of the disease. These findings harmonize with the outcomes documented in prior studies (Mohammed et al., 2017).

3.4 Association with Childhood Asthma

Examining the association of the *ApaI* polymorphism with childhood asthma, (Zhao et al., 2017) conducted a study encompassing 1,254 cases and 1,674 health controls. Their findings revealed an increased risk in various genetic models, with subgroup analysis indicating a relationship within the Asian population.

Moreover, the outcomes of the study by (Zhao et al., 2017) underscore a substantial correlation between the VDR gene ApaI (rs7975232) polymorphism and susceptibility to childhood asthma, as substantiated through the dominant model, recessive model, co-dominant model, and allelic model. In addition, the BsmI (rs1544410) polymorphism exhibited a modest

association with childhood asthma in the co-dominant model. Remarkably, these results challenge the findings of a previous study (Tizaoui et al., 2014), which proposed that the ApaI polymorphism might not be indicative of susceptibility to childhood asthma. Nevertheless, the FokI and TaqI polymorphisms emerged as contributors to asthma susceptibility, thereby providing corroborative evidence.

3.5 Association with Osteoporesis

Exploring VDR *ApaI* genotypes in postmenopausal women, (Dundar et al., 2009) observed three distinct genotypes: AA, Aa, and aa. Among these genotypes, individuals with the aa genotype exhibited significantly lower bone mineral density (BMD) values at the lumbar spine compared to those with the AA genotype. Additionally, postmenopausal women with the AA genotype displayed notably higher serum calcium levels. These observations suggest a potential contribution of the VDR *ApaI* gene polymorphism to the hereditary component of BMD, with potential implications for calcium absorption from the intestines.

Numerous endeavors have been undertaken to unravel the intricate relationships between VDR genotype, bone density, and diverse facets of calcium metabolism. However, the outcomes of these investigations have often yielded conflicting results. For instance, in the study (Ferrari et al., 1998), the distribution frequencies of VDR gene FokI, *ApaI*, *BsmI*, and *TaqI* polymorphisms were examined in conjunction with their association with bone mineral density (BMD) among postmenopausal women. The findings indicated that the co-genotyping of *ApaI* and *BsmI* or Taq I polymorphisms did not yield any association with BMD in postmenopausal women. Furthermore, a recent meta-analysis conducted by (Tizaoui et al., 2014) reported evidence of an association between the VDR *BsmI* polymorphism and BMD in the spine; however, no such association was observed with femoral BMD.

Chapter 4

Conclusion

Vitamin D exerts significant influence on immune system function, primarily mediated through its interaction with vitamin D receptors (VDRs). VDR gene variations can impact the immune response, potentially leading to joint damage, pain, inflammation, and stiffness associated with conditions like rheumatoid arthritis and breast cancer. Interestingly, individuals with breast cancer, rheumatoid arthritis, osteoporosis, or Periodontist disease often exhibit lower levels of vitamin D, suggesting its potential involvement in disease progression. However, the exact mechanisms are not fully understood.

Despite the connection between the VDR *ApaI* polymorphism and various disease communities, there are other factors at play that remain incompletely understood and may contribute to the development of these disorders in specific populations. Furthermore, the diverse and scattered nature of the available data indicates that the *ApaI* polymorphism's effects may vary depending on an individual's ethnic background. The susceptibility to these diseases cannot be generalized across different populations. Therefore, further research is necessary to establish a conclusive relationship between VDR *ApaI* and the aforementioned diseases. Factors such as population differences, age, gender, and other characteristics should be considered. The association between the VDR gene *ApaI* polymorphism and these diseases has been demonstrated in several distinct groups.

Future Aspect

VDR *ApaI* polymorphism has shown connections in various groups, additional research is required to validate its role in different diseases and gain a comprehensive understanding of the topic.

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