A Review on the Association of SNP at rs731236 of VDR Gene and Different Diseases in Various Ethnicity

By

Usrat Rifat Binte Rafique
19146063

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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/We have acknowledged all main sources of help.

Student's Full Name & Signature:

Usrat Rifat Binte Rafique
19146063

Approval

The thesis titled "A Review on the Association of SNP of at rs731236 of VDR Gene and Different Diseases in Various Ethnicity" submitted by Usrat Rifat Binte Rafique (191146063), of Summer, 2022 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

Supervised By:

Dr. Md. Aminul Haque
Associate Professor
School of Pharmacy
BRAC University

Approved By:

Program Director:

Professor Dr. Hasina Yasmin
Program Director and Assistant Dean
School of Pharmacy
BRAC University

Dean:

Professor Dr. Eva Rahman Kabir
Dean
School of Pharmacy
BRAC University

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

There is much of information on vitamin D's importance in bone metabolism, but less is known about how it affects other organs or systems. Vitamin D is receptor is found in the kidney, pancreas, prostate, gut, platelets, and immune cells where it is synthesizing 1-hydroxylase enzyme showing that it is actively connected in these cell populations and disorders related to them. Diseases like rheumatoid arthritis, Behcets Diseases, osteoporosis, allergic disease and renal dysfunction. The frequency of genotype and alleles of various VDR polymorphism with such disorders in Egyptian, Tunisian, Caucasian, Asian, German, Spanish and some other European population has proved to be connected. The only suggested treatment to maintain the homeostasis of Vitamin-d to regulate normal VDR activity is vitamin D supplementation though more research work should be done focusing VDR polymorphism related diseases and their treatment.

Keywords: Vitamin D; VDR; Polymorphism; TaqI; Autoimmune Disease

Dedication

A dedication to my parents who have been the pillars of my strength in every step of my life.

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List of Acronyms

VDR	Vitamin D Receptor
SNP	Single Nucleotide Polymorphisms
RA	Rheumatoid Arthritis
BD	Behcet's disease
LN	lupus nephritis
GWAS	genome-wide association studies
MODY	maturity-onset diabetes of the young
OP	Osteoporosis
AD	Autoimmune Disease
UC	Ulcerative Colitis
QOL	Quality of Life
ESRD	End Stage Renal Disease
DN	Diabetes Nephropathy
NL	Nephrolithiasis

Chapter 1

Introduction

1.1 Background

A crucial component for our health is Vitamin D as deficiency of vitamin D leads to many disorders related to different body organs. In recent days, many autoimmune disorders (AD) has found to be connected to Vitamin D level in body. However, there is lack of data on the relationship and treatment of these autoimmune disorders and the vitamin D levels required to maintain good health. As a matter of fact, Rheumatoid Arthritis is such a common autoimmune disease but still so many people are suffering from RA. It is commonly seen around us within the society, mostly among elderly people. Watching such scenarios from a close proximity has given me an inner quest to learn more about the autoimmune disease which has led me to take my thesis topic of Review on Relation of SNP in rs731236 in case of different diseases over various ethnicities where a sound knowledge on the association of VDR polymorphism and some different autoimmune diseases can be obtained. Many interesting researches has already been done in different ethnicities in relation to SNP of TaqI in patients suffering from different diseases. This review will help to summarize all those data of TaqI polymorphism and their relationship to different diseases.

1.2 Vitamin D in Bone Health

Among hundreds of importance's of vitamin D, the one that stands out the most is its activity in maintaining bone health. It is a key factor required for maintain the balance of minerals and skeletal structure. It is known as a secosteriod hormone which is important for Ca^{2+} absorption and bone development. This factor is related to bone mineral density (BMD). It is being found that vitamin D deficiency for a longer time leads to various bone disorders both in children and adult population. Dihydroxy vitamin D3 [1,25$(OH)_2$D3], active form of vitamin D in case of hormone, it is responsible for the function of vitamin D within our body which are regulated by the vitamin D receptor (VDR) (Ranganathan, 2009). There are different kinds of vitamin D, and each one works in a different way. Vitamin D is classified as a secosteroid the rings of it can be broken in sunlight. Calciferol is the form of vitamin D that works best. The body doesn't do much with other forms. Once vitamin D is made in the skin or eaten, it needs to be changed chemically in the liver and kidneys to make 1,25 dihydroxy vitamin D [1,25(OH)2D3], which is the form of vitamin D that works in the body. Active vitamin D acts like a hormone because it tells the intestines to do its main job, which is to help the body absorb more calcium and phosphorus (Cutolo et al., 2007).

1.2.1 Rickets

Normal bone development and mineralization requires ample calcium and phosphate must be available for. Rickets can be caused by inadequate mineralization at the growth plate. As long as a child's growth plates are open, rickets frequently develop. The two types of mineralization deficits are phosphopenic (hypophosphatemic) rickets and calcipenic (hypocalcemic) rickets, both of which are brought on by phosphate deprivation. The majority of the kids lacks from vitamin D. Based on how they react to vitamin D supplementation,

these kids may have higher vitamin D needs. Thus, children who are calcium deficient may have higher vitamin D requirements than expected (Mosaad et al., 2014).

1.2.2 Osteomalacia

Osteomalacia develops when the mineralization phase of bone remodeling is hampered, which is a disturbance in the physiological process of bone turnover. Osteomalacia is frequently caused by vitamin D insufficiency, and there is typically secondary hyperparathyroidism present as well. However, an absolute vitamin D deficit results in an increasing proportion of unmineralized osteoid replacing the bone. Weight-bearing bones start to bend as a result, which is invisible yet painful because it stretches the periosteum, causing the patient to feel limb discomfort. Because [1,25$(OH)_2$D] levels are low or nonexistent and because osteoid covers a major portion of the bone surface, calcium release from bone is impeded, the serum calcium may decrease (Christakos et al., 2020).

1.2.3 Stress Fractures

Stress fractures are frequent among new athletes and recruits. Although a number of predisposing factors have been proposed, the precise pathogenetic function is yet unknown. Changes in bone metabolism brought on by dietary and hormonal changes may have a significant impact on the pathophysiology of stress fractures by affecting both bone turnover and composition. Dietary vitamin D deficiency and other reasons related with low vitamin D levels, such as increased blood PTH concentration and lower bone mineral density, have all been linked to disease (Christakos et al., 2020).

1.2.4 Osteoarthritis

Osteoarthritis (OA) characterized by cartilage loss is a chronic degenerative condition. OA is viewed as a condition affecting the subchondral bone, synovial membrane, and cartilage. Although the disease's origin is unclear, recent research supports that an imbalance in subchondral bone remodeling may be what starts the deterioration process (Christakos et al., 2020).

1.3 Rheumatoid Arthritis (RA)

Rheumatoid arthritis (RA) is a systemic autoimmune disease that causes inflammation in the joints and other parts of the body. It is a long-term inflammatory disease that mostly affects synovial joints. It is often caused by a mix of genetics and the environment. Rheumatoid arthritis is different from osteoarthritis because immunity system attacks the synovial joints and joint linings in case of RA (Chauhan et al., 2022). If this condition is not treated for a longer period of time, it gets started in small peripheral joints, proceeds to involve proximal joints, and is frequently symmetric. Joint inflammation eventually results in joint degeneration due to cartilage loss and bone erosion. Early RA is characterized by symptoms that have been present for less than six months, while established RA is characterized by symptoms that have been present for more than six months. If left untreated, RA progresses, increasing mortality and morbidity (Chauhan et al., 2022). Among the eighty known types of diseases caused by autoimmunity, rheumatoid arthritis (RA) stands out. A chronic inflammation that can affect a variety of tissues and organs, including synovial joints and the cervical spine, characterizes it as a systemic collagen vascular illness. This condition affects 1% of the world's population, with women being more traumatized than men (Bharathi et al., 2021). The development of this degenerative condition typically occurs between the ages of 40 and 50, however it can happen at any age. The kind, quantity, and pattern of affected

joints vary depending on the individual. The frequency of swollen joints, the presence of autoantibodies in the blood, the intensity of the inflammatory process, genetic, environmental, dietary, and hormonal factors are only a few of the many things that affect how the disease develops (Bharathi et al., 2021).

Rheumatoid arthritis has no pathognomonic laboratory test, which makes early diagnosis of the condition difficult. To make the diagnosis and avoid crippling joint damage, a thorough clinical approach is necessary. A person suffering from Rheumatoid arthritis need both pharmaceutical and non-pharmacological remedies to be treated. Early treatment with disease-modifying anti-rheumatic medications is now considered standard of care. Despite receiving treatment, a large number of individuals Eventually, they lose their ability to work and get very sick. To enhance therapeutic outcomes, a thorough pharmaceutical and non-pharmacological treatment (physical therapy, counseling, and patient education) is necessary (Chauhan et al., 2022).

1.4 Vitamin-D Receptor (VDR)

Vitamin D is a steroidal hormone that binds to nuclear hormone receptor VDR. Vitamin D and VDR signaling is critical for controlling the growth and differentiation of immune cells, immune system stimulation by way of lymphocyte activation, and the production of cytokines, all of which may contribute to autoimmunity. Vitamin D is important for calcium metabolism and bone development, but it also has a play in how the immune system works. It also helps reduce inflammation and fights off infections. The VDR is found in multiple types of bone cells, but osteoblasts and osteocytes have the most of it. This makes them the main ones in charge of 1,25(OH)2D3 activity in bone homeostasis. (Bagheri-Hosseinabadi et al., 2020). Though considerably less frequently, VDR expression can also be found in osteoclasts and chondrocytes. As temporally controlled interactions between osteoblasts and osteoclasts

and between chondrocytes and osteoclasts maintain bone homeostasis, [1,25(OH)$_2$D3] can influence bone development and remodeling when VDR is demonstrated in all of these cell types and remodeling (Christakos et al., 2020). Several studies have suggested that VDR signaling plays a critical function in T-cell differentiation and function (Bagheri-Hosseinabadi et al., 2020). VDR is majorly positioned on immune cells including CD4+ T cells, CD8+ T cells, and antigen-presenting cells. When vitamin D2 or D3 enters, it creates complex with the vitamin D binding protein (VDBP) . This complex gets into the liver. Vitamin D is changed into 25-hydroxyvitamin D [25(OH)D] in the liver at position 25 (Mukhtar et al., 2019). The 25-hydroxyvitamin D (25(OH)D) is then taken to the kidney and then it get hydroxylated again by the 1-hydroxylase enzyme to produce 1,25 di-hydroxyvitamin D (1,25(OH)2D), which is the active hormone form. 1,25(OH)2D then binds to the VDBP to act on the target cell. After getting into the cell, it binds to VDR in the cytoplasm and forms a complex. This complex goes into the nucleus, where it forms a heterodimer with the retinoic acid X receptor. This increases the expression of vitamin D dependent genes that are important for bone and calcium metabolism (Mukhtar et al., 2019). After the hormone binds to the receptor it regulates the transcriptional activity of [1,25(OH)$_2$D3]- responsive genes by complexing with a vitamin-D response element located in the promoter region of target genes. The vitamin-D receptor (VDR) is a possible cause of many diseases, such as prostate cancer, urolithiasis, inflammatory bowel disease, Behcet's disease, atopic dermatitis, rheumatoid arthritis, etc. Vitamin-D is a steroid hormone that keeps calcium in balance and controls cell growth and differentiation in both normal and cancerous cells. Many epidemiological studies have connected low vitamin-D levels to an increased risk of prostate cancer. Because allelic differentiation affects the function of the receptor and D on the receptor's downstream effects, such as calcium absorption, excretion, and modulation of cellular proliferation and differentiation (Mittal et al., 2005).

1.5 VDR Polymorphisms

Patients with RA, OP, BD, LN, UC, and AD have been tested for polymorphic variants in osteoporosis candidate genes like VDR. Vitamin D (VD) is important for calcium homeostasis and for regulating the immune system. Polymorphisms in the VDR gene seem to affect whether or not someone with RA is likely to lose bone mass. VD and its similar substances work through the nuclear VDR, which is in charge of turning the action of the VD active form into something else. The VDR is a nuclear ligand-dependent transcription factor that, when combined with the hormone-active VD, controls the expression of many genes involved in inflammation and immune modulation. The VDR gene is found on both neuronal and glial cells of the immune system. VD binds to its receptor in the cytoplasm. This complex gets into nucleus and combines with retinoic acid X receptor to increase the synthesize of VD-dependent genes that are very important for calcium and bone metabolism. Different VDR polymorphism such as BsmI, ApaI, TaqI, and FokI, BsmI and ApaI are located into different sites. In exon 8 VDR polymorphism like BsmI and ApaI are located. In Exon 9, TaqI results in a silent codon alteration that boosts the stability of the VDR mRNA. The exon 2 location of the FokI polymorphism results in a protein with varied size; the shorter (424 aa) form is more active than the longer form (427 aa). Significant anti-infection and anti-inflammation properties of VD exist. Previous research revealed that VDR activity has a significant role in T cell growth, differentiation, and function. This is because T cells are critical for both the development of inflammatory disorders and protective immunity. Numerous autoimmune disorders, such as RA, osteoporosis, lupus nephritis, BD, and renal disease, could be brought on and spread by genetic variations of the VDR gene and low VD status (Tizaoui & Hamzaoui, 2015). When it comes to RA, the VDR gene is very commonly studied . This gene is on chromosome, and there are four polymorphisms—BsmI (rs1544410) and ApaI (rs7975232), TaqI (rs731236), and FokI—that show how different people are

(rs10735810). Even though we don't know what these four VDR polymorphisms mean in terms of how they work, it is thought that LD and more functional polymorphisms elsewhere in the VDR gene demonstrate the links in both VDR gene polymorphisms and autoimmunity (Song et al., 2016).

1.6 VDR Polymorphisms and Diseases

Numerous studies have shown that VDR polymorphisms, such as FokI (rs10735810), BsmI (rs1544410), ApaI (rs7975232), and TaqI, are linked to a higher risk of cancer (rs731236) Vitamin D is thought to control the immune system because it helps stop the production of interleukin-2 (IL-2), makes antibodies, and makes lymphocytes multiply. Because of this, VDR does have a wide range of diseases, and the severity of each disease is linked to different polymorphisms.

1.6.1 Systemic Lupus Nephritis

Systemic lupus erythematosus is an AD that affects many parts of the body, most often the kidneys. Lupus nephritis (LN) is mostly found as the cause of kidney damage in people with systemic lupus erythematosus. It is also a significant cause of illness and death. The causes of LN are not all the same. This difference is probably caused by genetic and environmental reasons. Even though we know more about what causes LN, treatment hasn't changed much, and the risk of kidney failure is still too high (Parikh et al., 2020).

1.6.2 Behcet's Disease

Behcet's disease (BD) is a chronic relapsing-remitting vasculitis that hasn't been figured out yet. Because it has the potential to encompass arteries and veins of all diameters, it can impact practically all organ systems and cause considerable organ-threatening morbidity and

mortality. It is commonly known as the "silk road" illness and occurs everywhere. Although human leukocyte antigen and non-human leukocyte antigen correlations have been found in genome-wide investigations, the aetiopathological pathways of illness progression in BD remain poorly understood. The aetiopathogenetic mechanisms that cause the development of the disease may be influenced by genetic and environmental variables, suggesting the autoimmune and auto-inflammatory nature of BD (Nair & Moots, 2017). Behcet's disease (BD) is a systemic inflammatory illness that can cause lesions in the mucocutaneous, ophthalmic, vascular, gastrointestinal, musculoskeletal, skin, and central nervous systems, among other symptoms. A number of genetic variables are shared by RA and BD, according to genome-wide association studies (GWAS). Several studies have found that BD and RA patients share various VDR polymorphisms, including FokI (rs10735810), BsmI (rs1544410), ApaI (rs7975232), and TaqI (rs731236) (Tizaoui et al., 2014).

1.6.3 Allergic Diseases

Multiple studies have already revealed that changes in the vitamin D receptor (VDR) gene are linked to allergic reactions. About 30% of the general population has allergies like asthma, atopic dermatitis, and allergic rhinitis. Even though anti-allergic drugs and corticosteroids may aid in symptom alleviation and illness management, allergic diseases nevertheless significantly affect patients' quality of life. Furthermore, a large number of patients who are resistant to current therapy will eventually experience life-threatening co-morbidities. Even now, we still don't fully comprehend the pathogenesis of allergic problems. But it was abundantly clear that genetic elements were important for its growth. First, how common allergy diseases are in different types of contact scenarios. Different genetic backgrounds and immunological investigations were likely contributing factors to the variations in illness occurrence across various groups. Second, genetic association studies have previously

identified and confirmed a number of genetic loci that are susceptible to allergic disorders. Vitamin D may activate macrophages, boost Th1 cytokine production, and suppress Th2 cytokine production, according to a number of prior basic investigations. Because Th2-related cytokines like interleukin-4 (IL-4), IL-5, IL-10, and IL-13 are known to be important in the start and growth of allergic reactions, it was thought that the metabolic pathway for vitamin D would also play a role in the cause of allergic disorders. Vitamin D binds to the vitamin D receptor to do its work in the body (VDR) (Zhang et al., 2020).

1.6.4 Cardiovascular Disease

Recent findings have shown more than once that we know a lot about four VDR polymorphisms: FokI, BsmI, ApaI, and TaqI. We also know a lot about Cdx2, poly (A), A-1012G, and Tru 91, but they are rarely studied. VDRs are found in all of the main types of cardiovascular cells, such as vascular smooth muscle cells (VSMC), endothelial cells (ECs), cardiomyocytes, platelets, and most immune cells. This means that VDR gene polymorphisms may have an effect on CVD. Also, the VDR is a key part of controlling the expression of proteins like renin, endothelial nitric oxide synthase, and NADPH oxidase that help control the heart and blood vessels (NOX) (Abouzid et al., 2021).

1.6.5 Probiotics and Gastrointestinal Diseases

Damage to the intestines in colitis models is linked to how much vitamin D a person gets. IBD patients often don't get enough vitamin D. Vitamin D deficiency has been known to be a risk factor for people with Crohn's disease since the early 1980s. In a group of people with IBD, those who didn't get enough vitamin D had worse symptoms of Ulcerative colitis (UC) and a lower quality of life (QOL). In a more recent study, it was found that taking 1000 IU of vitamin D3, 1200 mg of calcium, or both every day did not decrease the probability of

colorectal adenomas coming back after they were removed for 3 to 5 years. Several things can make it harder to absorb vitamin D, such as not getting enough sun, having dark skin, being overweight, or having trouble absorbing vitamin D or changing it into its active form. Due to how vitamin D affects the immune system, not getting enough of it makes you more likely to get GIT diseases. It is likely that low levels of vitamin D lead to problems with the intestinal barrier, mucosal damage, and susceptibility to infectious agents, which affects the development and maintenance of gut homeostasis. 1,25(OH)2D3 and VDR may keep junction complexes together and keep the intestine from getting hurt (Shang & Sun, 2016).

1.6.6 Renal Disease

VDR is a transcription factor that is turned on by 1,25(OH)2D and responds to ligands. Reports say that a lack of VDR turns on the renin-angiotensin system, which causes too much angiotensin II to damage the renal parenchyma and raise the risk of getting a kidney disease. Because VDR is so important to keeping the kidneys working well, a lot of research has been done to see if there is a link between polymorphism and the risk of getting renal disease. ApaI and TaqI are VDR polymorphisms that have been studied a lot to see if they might be linked to End-Stage Renal Disease (ESRD) (Hussain et al., 2019).

1.6.7 Gestational Diabetes Mellitus

It has been almost 50 years that postpartum hyperglycemia, but still there is no presence of universal agreement on the threshold hyperglycemic levels that require a diagnosis of "gestational diabetes mellitus" (GDM) and, consequently, therapy during pregnancy. Today, more and more young women are showing signs of diabetes and suffering from undetected hyperglycemia, making (GDM). The most common health complication during pregnancy. Maternal overweight and obesity, a later reproductive age, a history of GDM, a family history

of type 2 diabetes mellitus, and racial/ethnic background all contribute significantly to the likelihood of developing GDM up (McIntyre et al., 2019). Most of the time, a diagnosis needs an oral glucose tolerance test (OGTT). In other parts of the world, a non-fasting glucose challenge test (GCT) is used to figure out which women need a full OGTT. Diet habits and more physical activity are the main ways to treat GDM. When normal blood sugar levels are not reached, medication, mostly insulin, is used. Metformin and glibenclamide are the two main oral medications used to treat diabetes. Glyburide is also used in many countries. The treatment improves the immediate outcomes of pregnancy by reducing problems like excessive fetal growth, obesity, and high blood pressure. GDM makes both the mother and the fetus more likely to have long-term problems, such as obesity, poor glucose metabolism, and heart disease. Even though most of the world doesn't use preventive measures, it's still hard to give mother and child the best care during long-term follow-up (McIntyre et al., 2019).

1.7 Objective

Study and Review on Relation of SNP in TaqI (rs731236) in case multiple diseases will give a deeper insight about diseases like lupus erythematosus, Behcets disease, Rheumatoid arthritis, osteoporosis, atopic dermatitis and its relationship of SNP in a more confined way. This will narrow down all the findings of previous research that had been conducted in different regions over people belonging to various ethnicity which will give us a chance to understand where we should concentrate more to research further in the field of VDR polymorphisms. As this review article highlights the connection of VDR polymorphism activity in individuals with related diseases, hence we can look how genes and alleles are actually affecting the patients. Summarizing all this knowledge will aware us about the current condition of research on this field and how much we should do to bring out a

significant positive result from all these research woks. Also, summarizing the research results conducted on different ethnicity will also help to understand the best way to treat those group of people. It will inquisitee more research work to find suitable treatment for patients suffering from diseases that are being affected by VDR genes.

Chapter 2

Materials and Methods

Review on Relation of SNP in TaqI (rs731236) in case of different diseases is the focus topic of this paper. Keywords that were used for retrieval of the article: “Vitamin D”, “VDR”, “VDR polymorphism”, “Rheumatoid Arthritis”, “TaqI”, “rs731236”, “Behçet's disease”, “Lupus”, “Renal Disease” and different population in PubMed, Medline, Science direct, Nature and Google Scholar databases. These mentioned sites were used to maintain the authenticity of the articles from where I collected information and data to write my review paper. A request for a reprint was issued to the appropriate author of each piece whose full text was not accessible after retrieving all of the free complete texts. While retrieving data from different articles it was ensured that full texts of the articles were available, the publications of interest were conducted on different ethnicity and DNA and alleles were prioritized. After ensuring the mentioned concerns, I read all the articles and tried to found the connection of SNP of VDR and its effect on patients from different diseases. As, my focus was mainly TaqI (rs731236) polymorphism I selectively looked for their result in my article. After studying over many articles and retrieving data from 25 articles I came to understand that VDR polymorphism has connection with certain diseases due to their allele and genotype distribution. I tried to summarize the articles in a simple way so the readers can understand them easily. Data of each study such as author’s name, the year when the study was conducted, ethnicity of the subjects, distribution of genotype and allese, etc., was calculated.

Chapter 3

Result & Discussion

3.1 Result

Since it was found that maximum cells have VDR and that some other also have the enzymes to make vitamin D active, there has been a lot of interest in the possible biological effects of VDR. Several pieces of evidence show that VDR gene variants may be involved in autoimmune diseases (Mosaad et al., 2014).

In addition to postmenopausal OP females and healthy controls, Egyptian patients also showed higher connection of the FokI (rs10735810), BsmI (rs1544410), ApaI (rs7975232), and TaqI (rs731236) genotypes and alleles. People with the disease and healthy controls showed highly significant differences in the allelic distribution of BsmI, TaqI, and ApaI polymorphisms (P 0.001) and (P = 0.025), respectively. After applying Bonferroni correction (Pc = 0.1), however, the significance of the FokI SNP was no longer present. Patients with RA had a higher frequency of the b allele of BsmI and the T allele of TaqI than controls did, suggesting that these alleles may have a susceptibility impact to RA in our group. Both the genotypic and allelic distribution of the FokI polymorphism, as well as the frequency at which it was found, suggested no association. The frequency of the TaqI genotype TT was found to be significantly greater in RA patients compared to healthy controls (Pc = 0.05) when the genotype distribution of the two groups was compared. VDR gene polymorphism in patients who are also suffering from postmenopausal osteoporosis showed a statistically significant association for the Bb genotype (P = 0.04), FF genotype (P = 0.02), Ff genotype (P = 0.04), and TT genotype (P = 0.03), all statistically significant values were lost after Bonferroni correction. None of the clinical, or laboratory characteristics of RA patients were

linked to the TaqI genotype. Here, we evaluated the spread out of VDR alleles and genotypes in postmenopausal women with osteoporosis to those of healthy controls, as well as the frequency of alleles and genotypes of distinct VDR SNPs in connection to the presence or absence of OP in RA patients and postmenopausal women. Increased prevalence of the BB and tt genotypes in healthy controls compared to OP females (P = 0.03, P = 0.029, respectively) suggests that these genotypes may offer protection against the onset of osteoporosis. However, after taking into account the corrections, the P values still did not attain statistical significance. VDR allele and genotype distribution were not associated with RA risk in this study (Mosaad et al., 2014).

In the Spanish population, TaqI genotypes and disease onset were found to have a marginally significant but modest correlation. Patients with the genotype 'tt' demonstrated an earlier onset form of rheumatoid arthritis than the combined 'TT' and 'Tt' genotype groups (P = 0.04). Although both males and females showed this connection between TaqI polymorphism and disease onset, statistical significance was only attained in the female group (P = 0.05). When female patients were categorized based on SE status, those with the 'tt' genotype showed the earliest form of disease onset (P = 0.04). There weren't enough men in our sample to use for a stratification analysis. Polymorphism in VDR genotypes revealed by BsmI was in substantial linkage disequilibrium with the TaqI restriction endonuclease site, and the B allele was linked to it by 96%, as has been observed in other populations (Garcia-Lozano et al., 2001).

In German population, Distribution of TaqI and BsmI VDR genotypes was different in patients and controls when comparing single polymorphisms, reduced in number and occurrence BB and tt genotype with larger frequency of heterozygotes in RA patients (p=0.026 for BsmI, p=0.017 for TaqI. Because of the explorative approach no correction for

multiple testing was made. Assuming a level of significance of p = 0.015 according to the three polymorphisms tested, the difference in distribution of BsmI and TaqI polymorphisms were no longer significant, although the difference in TaqI genotypes was close to statistical significance. No difference in genotype distribution was observed between seropositive and seronegative patients. No association betweenn genotype and age at onset was found. Furthermore we detected linkage between b and T as well as between B and t alleles (p = 0.0001). In patients and controls taken together, 93% of individuals homozygous for the t genotype also were homozygous for the B allele. We detected no difference concerning linkage between the patient and control groups and no linkage between FokI genotypes and BsmI or TaqI genotypes (Goertz et al., 2003).

Among Asian and European population, the meta-analysis work done on relation between VDR polymorphism and allergic diseases. The findings of this analysis showed that Polymorphisms in the VDR rs7975232 ApaI, rs1544410 BsmI, and rs731236 TaqI genes were linked to an increased risk of developing allergy disorders in some people. The VDR gene polymorphisms at rs7975232 ApaI, rs1544410 BsmI, and rs731236 TaqI were not shown to be significant. Polymorphism in the vitamin D receptor gene (VDR) at position rs2228570 in human FokI. If we only looked at people who had asthma, we discovered that the rs1544410 BsmI polymorphism in Caucasians and the rs731236 TaqI polymorphism in Asians were both beneficial. That environmental factors can influence both allergy factors and VDR polymorphism is a drawback of this study (Zhang et al., 2020).

To investigate the relationship between the entire study was depended on information gathered from 2777 case study group and 3522 healthy controls, where different population such as Chinese, Irish, Croatian, Indian, Spanish and Italian were included. Under an allele contrast fixed effect model, the VDR TaqI C-allele was linked to renal illnesses when DN, ESRD, and NL were all taken into account (p = 0.008). Taql C- allele was shown to be linked

with ESRD, as evidenced by subtype analysis (p = 0.03) onset (Hussain et al., 2019). Turkish population demonstrated the strongest connection between Vitamin D Receptor (VDR) TaqI Polymorphism and Renal Disease among the various ethnic groups (C vs. T, p = 0.04) . According to the analysis, leaving out this particular study had no impact on the overall result of illness onset (Hussain et al., 2019).

Concerning the associations between VDR polymorphisms and RA. A study of the TaqI of VDR found no association among RA and the T allele (P = 0.288) in any of the study participants (Lee et al., 2011). However, this revealed no link among RA and the VDR TaqI T allele in Europeans or Asians. Moreover, utilizing recessive or dominant models or contrast of homozygotes, there was no connection between RA and the VDR TaqI polymorphism. However, no association between LN and TaqI was discovered; instead, only the BB polymorphism was revealed to be related to LN. The study using the allele contrast, recessive, dominant, or additive models could not find any relationships between the TaqI polymorphism and RA in the general population or in populations from Europe or Asia (Lee et al., 2011).

In French population, we investigated the connection between three VDR polymorphisms (FokI, BsmI, and TaqI) and RA and discovered that genotype FF and allele F appeared to be linked to RA susceptibility. No interrelation between the TaqI polymorphism and Rheumatoid arthritis has been found after conducting a research work (Maalej et al., 2005).

In Tunisian population, the relationship of VDR ApaI and TaqI polymorphisms with BD and RA risks was investigated. The frequency of genotypes for VDR polymorphisms did not deviate significantly from HWE (P > 0.05) (data not shown).The connection in both TaqI polymorphism and BD were marginal under the codominant (P = 0.078) or the recessive (P = 0.058) models (Tizaoui et al., 2014). Despite this, when the data were broken down by sex,

we still found no correlation among the VDR TaqI polymorphism and BD risk in either males or females ($P > 0.05$). For RA, there were no statistically significant variations in the distribution of genotype frequencies between patients and controls for either the ApaI or TaqI polymorphisms (Tizaoui et al., 2014).

For Caucasian population the connection of 3 different VDR polymorphism BsmI, ApaI, TaqI and FokI polymorphisms and bone loss has been studied. BMD measures at the hip and lumbar spine were taken in a research work of 232 Caucasian individuals (160 females and 72 males) with early RA at baseline and every 12 months for three years (Ranganathan, 2009). All patients who had their genotypes for the VDR TaqI polymorphism tested at baseline, 3, 6, and then yearly for CRP levels, swollen joint counts, joint discomfort, functional status, and disability. The polymorphism was also genotyped in 70 healthy controls. Between RA patients and controls, Neither the frequency nor the distribution of the TaqI genotype varied significantly. Age, gender, height, weight, and the severity of the disease were similar in RA patients bearing the VDR TT and tt groups (Ranganathan, 2009).

3.2 Discussion

In Egypt, the presence of TaqI polymorphism in RA patients, postmenopausal OP patients and healthy controls has been studied. Where T alleles of TaqI was larger in frequency RA patients, postmenopausal women than healthy controls which is why it was suggested that T alleles were susceptible to RA. To better understand the association of VDR and RA-related OP, we investigated the allele and genotype frequencies of several VDR SNPs by comparing patients with OP in RA patients and postmenopausal individuals. The distribution of VDR alleles and genotypes in postmenopausal OP individuals and healthy persons (Mosaad et al., 2014). The spread out of tt genotypes was higher in OP females than in healthy controls, indicating that these genotypes may be preventative of osteoporosis development. B alleles of

BsmI showed significant connection but FokI failed to demonstrate any relationship. It was also established during this test that The TaqI genotypes were not associated with any of the demographic, clinical or laboratory parameters of RA patients (Mosaad et al., 2014).

In Spanish population, it has been found that patients with vitamin D receptor polymorphisms have a slightly increased risk of developing rheumatoid arthritis in presence of the *Taq*I alleles (tt) reveal symptoms of rheumatoid arthritis. These genotypes are linked with rapid loss of density in bones of female patients with RA as well as in postmenopausal women. Although the etiopathology of RA is not known even now, illness vulnerability and the ways in which it manifests clinically are known to be strongly influenced by genetic factors, which may themselves be complicated. (Garcia-Lozano et al., 2001).

In specific genetic comparisons, the TaqI polymorphism is linked to allergy disorders. We further validated the favorable outcome for the rs731236 TaqI polymorphism in atopic dermatitis by doing subgroup analysis by disease. In addition, substantial relationships were found when participants were divided into groups based on their ethnicity. Asiatic TaqI polymorphism (Zhang et al., 2020).

The allele contrast model for renal illness indicated notable connection between both the VDR TaqI polymorphism and ESRD. But no connection is found between DN, NL, and TaqI polymorphism. Studies have looked into how variants in the VDR gene affect the etiology of renal illness. TaqI and ApaI polymorphisms are two of the most extensively researched. It was found that C alleles of TaqI polymorphism has association with renal diseases though at the end of the meta-analysis study it was established that only Turkish population has strong association with TaqI C, on other population TaqI C do not have any significant effect (Hussain et al., 2019).

We have expanded on our earlier research to examine the influence of TaqI polymorphisms, which are found in the 30UTR site of the VDR gene, on Tunisian population danger of developing BD and RA (Tizaoui et al., 2014. The study represents the first to look into the relationship between TaqI polymorphisms and BD in Tunisian population. The findings demonstrated a weak relationship between TaqI polymorphism and a reduced propensity for BD development. The TaqI polymorphism may give a benefit in fending off BD in elderly adults, according to some speculation. However, there is no evidence linking VDR TaqI and ApaI polymorphisms (Tizaoui et al., 2014).

After researching it was found that there is no relationship between TaqI polymorphism and RA patients in French population (Maalej et al., 2005).

These studies' findings confirm a link between particular VDR alleles and RA-related bone degradation. Surprisingly, the TaqI t allele was not related with localized bone loss in RA, but rather with increased widespread bone loss. Familial RA and RA with an early onset were both associated with the FokI and TaqI polymorphisms, respectively. Together, our results suggest that vitamin D has an immunoregulatory function that is mediated by VDR and affects RA disease susceptibility and bone loss. Thus, it is anticipated that gene polymorphisms that directly affect calcium and vitamin D metabolism, such as VDR, will have an impact on bone loss in RA. TaqI polymorphism shows no susceptibility to SLE (Ranganathan, 2000).

3.3 Treatment Aspects

Many research papers and meta-analysis work has been done from where the results and discussions are narrowed down to that depending on people's ethnicity the effect of polymorphism varies on different diseases. Also, none of these research works has been able to come up with the effective solution or a better treatment. The only way to prevent such autoimmune disease is to take vitamin D supplementation if required regardless of ethnicity.

Chapter 4

Conclusion

We can observe that many research works have done over the years over different population and different polymorphisms of VDR has gone through under investigation over its connection to multiple disease. For, TaqI polymorphism research work has been done on Egyptian, Spanish, German, Tunisian, French, Caucasian population over diseases like rheumatoid arthritis, Behcets diseases, osteoporosis, renal problem, LN, Atopic dermatitis to compare and understand the presence of TaqI VDR Alleles both homozygous and Heterozygous among healthy controls and patients suffering from these diseases. Most of the population except French population proven to have some significanc of TaqI polymorphism. But the number was not notable enough apart of atopic dermatitis in Asian population that the knowledge could be established in a cohort way. Thus, TaqI polymorphism has an effect among diseases effected by VDR but further study and research work needs to be done in other population to establish the knowledge concretely.

Future Aspects

Over the decades, many researches have been done but all these data are not enough to prove TaqI polymorphism and their association with the VDR diseases. To build an acceptable evidence further research works need to be done on a larger scale of population

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