

## CYP24A1 Polymorphism Effect on Chronic Drugs Administration and Development of Osteomalacia: A Review Article

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### ABSTRACT

**Osteomalacia is a condition that causes bone thinning, which is frequently caused by a vitamin D deficiency. Vitamin D aids in the formation of the body's bones, therefore when levels are low, the bones are not as strong as they should be. Muscle weakness, bone discomfort, and a waddling stride are some of the symptoms of osteomalacia. The lower back hips, and legs are particularly vulnerable to pain. The weakening of the bones may make them more susceptible to fracture. Osteomalacia may be induced by a lack of sun exposure or a lack of vitamin D in the diet.**

**Bone metabolic problems, cancers, cardiovascular illnesses, and diabetes are all linked to a lack of 25OHD. Also linked to autoimmune illnesses and mental problems. Vitamin D is one of the most important minerals for human health.**

**Keywords-** osteomalacia, CYP24A1, vitamin D, Diabetic, Hypertention patients and Epilepsy, polymorphism.

osteoid thickness is at least 15  $\mu\text{m}$ , and the mineralization lag time is at least 100 days<sup>[8]</sup>. Further, during the early stages of osteomalacia, histomorphometry is required to evaluate the extent of bone loss and skeletal abnormalities that have occurred.

The Cytochrome P450 (CYP) superfamily encompasses integral membrane, heme-thiolate proteins engaged in producing and breaking numerous compounds and substances inside cells. CYP enzymes have a role in the metabolism of several endogenous<sup>[9-10]</sup> chemicals including "steroids, bile acids, eicosanoids, cholesterol, vitamin D, and neuro-transmitters, as well as steroids, bile acids, eicosanoids, cholesterol, vitamin D, and neuro-transmitters". In addition to the CYPs. There are 57 human CYP isoenzymes mostly CYP2C, CYP2D, CYP2E, CYP2F, CYP2A6, CYP2A13, CYP2A9, CYP2C9, CYP2C19, CYP2C19, CYP2C29, CYP2C39, CYP2C40, CYP2C46, CYP2C55, CYP2C73, CYP2C81, CYP2C82, CYP2C86, CYP2C95, CYP2C96, CYP2C101, CYP2C111, CYP2C113, CYP2C122, CYP2C129. CYP proteins are often involved in phase I reactions, which metabolise endogenous compounds and perform catabolic and anabolic transformations. However, CYP proteins in the endoplasmic reticulum are mostly involved in phase II reactions, the many types of enzymes in a manufacturing process are organised into families and subfamilies<sup>[11-12]</sup>. For every CYP, a family identifier is allocated to the particular subfamily within the gene group, a unique letter to represent the subfamily, and a numeric value which is associated with the particular gene in the subgroup. CYP activity displays intra- and inter-ethnic, as well as intra- and interindividual genetic differences. While each CYP gene presents a somewhat different physical variant, these polymorphisms substantially affect the activity of the enzymes<sup>[13]</sup>.

Vitamin D is created by 7-dehydrocholesterol in the skin when exposed to ultraviolet radiation. Band B (UVB) uses this energy to transform the molecule into cholecalciferol, which is then rendered inactive in the body. The majority of systemic Vitamin D, up to 90%, is created via skin synthesis while a mere 10% is obtained through dietary consumption. Diabetes may be caused by 25-hydroxyvitamin D insufficiency. 1,25 (OH) 2D3 supplementation may aid in the recovery of normal glucagon levels. Vitamin D helps to synthesise neurotransmitters, contribute to inflammation, and

### I. INTRODUCTION

Over the course of history, rickets and osteomalacia have been associated with vitamin D insufficiency, going all the way back to the 17th century. While most often considered a disorder of bone density, osteomalacia literally means "soft bone." The four primary forms of osteomalacia<sup>[1-4]</sup> may be described as follows: Osteomalacia, which may be primarily defined as a mineralization deficiency, has several manifestations that vary based on osteoid thickness interactions with both osteoid surface and mineral apposition rate. It is true that strictly speaking, an increase in the total surface or thickness of osteoid alone does not really meet the definition of osteomalacia as it has been historically characterized<sup>[5-6]</sup>. Excess osteoid deposition may occur in numerous illnesses, such as situations of elevated bone turnover, enzyme abnormalities, and matrix diseases. Currently, the vast majority of physicians<sup>[7]</sup> believe that pseudofractures don't show characteristic radiological findings. As a result, osteoid volume is at least 5 percent, uncorrected

regulate calcium.

There is evidence to show that 1,25(OH)<sub>2</sub>D<sub>3</sub> (1,25-dihydroxycholecalciferol) may cause an increase in calcium binding protein expression. In addition, it may help boost levels of serotonin in the brain. Low levels of vitamin D have been linked to neurocognitive impairment, dementia, depression, and Alzheimer disease. As it affects the immune system and anti-fibrotic effects, vitamin D may be involved in the pathophysiology of chronic liver disorders.

## II. ROLE OF CYP24A1 IN VITAMIN D CATABOLISM

CYP24A1 is a mitochondrial inner membrane P450 that plays a role in the breakdown of vitamin D. It may be present in a variety of tissues, including the kidney, bone, skin, and the gastrointestinal system<sup>[16]</sup>. CYP24A1 hydroxylates 1,25(OH)<sub>2</sub>D<sub>3</sub> at several positions on the 1,24 position or the 1,24 or 1,25 positions, and these hydroxylation reactions result in the production of the 1,25(OH)<sub>2</sub>D<sub>3</sub>-26,23 lactone and the catabolite of calcitric acid, respectively. Another thing to note is that CYP24A1 alters the 25(OH)D<sub>3</sub> metabolite into 24,25(OH)<sub>2</sub>D<sub>3</sub>, which is then turned to calcitric acid, a water-soluble form of the ion. CYP24A1 has a considerable influence on enzymatic activity through many biochemical and genetic influences. The first step in this process is that the hypocalcemic state suppresses Cyp24A1 expression<sup>[17]</sup>, which in turn inhibits its expression via the disruption and suppression of its mRNA turnover. Several research studies have shown that PTH reduces CYP24A1 expression and enzymatic activity. The consequence of this regulatory action is

based on both transcription and post-transcription modification. Although small elevations in PTH stimulate a moderate rise in CYP24A1 promoter activity, they also have a major post-transcriptional influence on CYP24A1 mRNA stability, accelerating its degradation<sup>[18]</sup>. Despite many efforts, there is currently no way to identify the PTH response components in the CYP24A1 gene specifically, and a lot has to be revealed on the regulation mechanism. While the PTH inhibitory impact was detected in other non-renal tissues, such as the gut and epidermis, this was not shown in other extra-renal tissues such as the kidney. The opposing impact is influenced by the 1,25(OH)<sub>2</sub>D<sub>3</sub>, which controls its own production and causes Cyp24a1 expression to rise by means of a positive feedback loop that stimulates its expression<sup>[19-20]</sup>. Also, “the fibroblast growth factor 23 (FGF23), as well as its co-receptor α-Klotho, may favourably affect CYP24A1 activity in response to hypercalcemia and hyperphosphatemia. Because of its critical involvement in regulating the levels of 1,25(OH)<sub>2</sub>D<sub>3</sub> in the circulation, the extent of research into CYP24A1's significance in this regard has been widespread<sup>[21-22]</sup>. Mice lacking the CYP24A1 gene showed a much greater degree of impairment in 1,25(OH)<sub>2</sub>D<sub>3</sub> and 25(OH)D<sub>3</sub> pharmacokinetics than did mice that were heterozygous for the CYP24A1 gene. Additionally, the loss of function mutations in the CYP24A1 gene lead to the rise of both 25(OH)D<sub>3</sub> and 1,25(OH)<sub>2</sub>D<sub>3</sub> levels”, resulting in the increased intestinal absorption of calcium and bone reabsorption. IHH symptoms are primarily the result of the hypercalcemic state, as the resultant hypercalcemic phenotype.

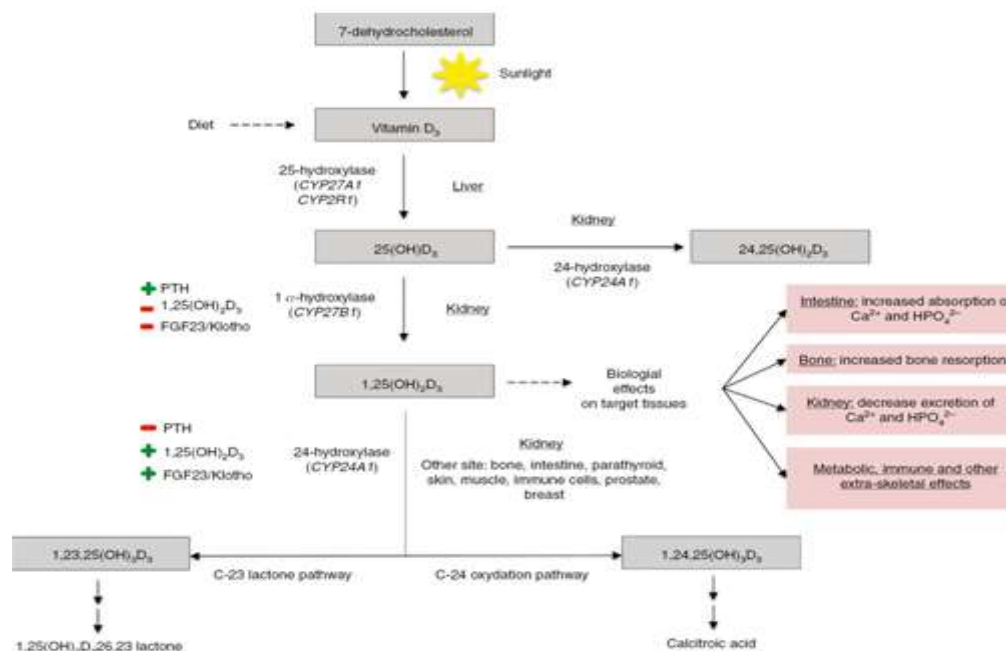


Figure 1: Vitamin D3 pathway overview and CYP24A1 physiological function.

#### **CYP24A1:**

The cytochrome P-450 CYP24A1 is a mitochondrial mono oxygenase that takes on a vital role in calcium homeostasis and regulates vitamin D3. It is called 24-hydroxylase (EC 1.14.15.16) because it catalyses the hydroxylation of vitamin D3 to 24-dehydrocholesterol (also known as 1 $\alpha$ ,25-dihydroxyvitamin D3). The side chain of vitamin D3 is hydroxylated, resulting in calcitric acid and other metabolites released in bile<sup>[23]</sup>. For the first time, in the mid-1970s, 25-hydroxyvitamin D3-24-hydroxylase, a mitochondrial enzyme that catalyses the decomposition of 25-hydroxyvitamin D3 into 24-hydroxyvitamin D3 and 24-OH-D3, was demonstrated in the kidneys. In the late 1980s, it was only later that researchers discovered the enzyme also occurs in the 24-hydroxylation of 25-OH-D3. Extensive scientific research that took place over the next 35 years has established that CYP24A1 is the aftereffect of 24-OHase. The cytochrome P450 enzyme CYP24A1 carries out the two major hydroxylation reactions of 25-OH-D3 and 1,25-(OH)2D3 to produce the corresponding hydroxylated metabolites that go to the common bile acids, such as calcitric acid, and the less water-soluble bile acid 26,23-lactone. Also have a key influence in enzyme activity<sup>[24]</sup>. The CYP24A1 protein is reliant on PTH and FGF for its translation. IRES, as a reaction to the current inflammatory condition, begins to circulate in a more polysomal form. It may also be connected to the risk of cell-mediated immunological processes in multiple sclerosis and inflammatory bowel disease. Increased expression of CYP24A1 and CYP27B1 followed by increased inflammation in inflamed colonic tissues in IBD patients causes the loss of 25(OH)D, putting downward pressure on the vitamin D status. As a result, it is very necessary<sup>[25]</sup> for the management of inflammations. One group included 45 ulcerative colitis patients genotyped for 45 SNPs who were part of the 1000 Genomes Project, while the other group consisted of 504 East Asians who were not part of the 1000 Genomes Project. However, it was shown that the allele frequencies were correlated with the illnesses, although this link was not significant<sup>[26-27]</sup>. The findings indicate that individuals who are homozygous for these genotypes are also at an increased risk of developing colon polyps and colon cancer, as well as having small intestine haemorrhage tied to low-dose aspirin usage. The 3' poly microsatellite repeat is thought to affect the stability of CYP24A1 mRNA, and this may lead to alteration of the methylation of the 3' UTR.

Furthermore, Rs6068816 was associated with

the likelihood of UC, demonstrating a close link between the two. In that case, or if it is a yes, rs6068816 C against T will be high again. And therefore, because these findings show that rs6068816 T is a major risk factor for UC, we can say with confidence that it also increases the risk of UC. The rs6068816 gene alteration will not affect the CYP24A1 protein's amino acid residues; however, it may affect intron splicing. Multiple SNPs in CYP24A1 and other genes associated with vitamin D metabolism and signalling have been shown to be significantly associated with UC in Asians. However, their effectiveness is unproven. According to the findings, SNPs in CYP24A1 may have a role in the development or development of UC, rather than just resulting<sup>[28-29]</sup> from a breakdown in the UC pathway. Although the mechanisms behind vitamin D's participation in immune-mediated diseases remain unknown, it is possible that it is linked to vitamin D metabolism and signalling. Vitamin D's effectiveness in immune-mediated diseases has been shown in both in vivo and in vitro studies. Less efficient colon bacterial clearance has been shown to be associated with inadequate vitamin D levels, according to the findings. The UC seems to be connected to CYP enzymes in vitamin D metabolism. Thus investigations on these enzymes should concentrate on the UC.

### **III. OSTEOMALACIA'S BIOCHEMICAL AND HISTOLOGICAL ADVANCEMENT**

The process of developing osteomalacia from vitamin D deficiency occurs in three stages, as shown by the following biochemical breakdown: In the first stage, there are normal levels of calcium and phosphate in the blood, and there are high levels of alkaline phosphatase., which is caused by an increase in PTH. Here, bone histomorphometry simply illustrates how the extra PTH from the disease state contributes to the enlargement of the bone, since there is no apparent mineralization issue<sup>[30-31]</sup>. There is a decrease in serum calcium and phosphate levels in the second stage, accompanied by a rise in both serum PTH and alkaline phosphatase levels. This occurs alongside normal or low levels of serum 1,25(OH)2D due to the amount of its substrate (also known as vitamin D3). The last stage, when low levels of calcium and phosphate are found coupled with secondary hyperparathyroidism and mineralization of bone matrix stops, is when severe hypocalcemia and hypophosphatemia are typically present as well as

increased levels of secondary hyperparathyroidism.

Some people's inadequate intake of vitamin D and less sunlight exposure contribute to their illness. Others avoid sunlight to prevent getting ill and then wear sunscreen with a high SPF. Other people may avoid sunlight because of their religion or culture, so they wear clothing that completely covers their skin. Osteomalacia, or Osteomalacia I, is due to a loss of Vitamin D in the intestines, which means that elderly people tend to have

lower levels of Vitamin D in their skin, albeit this isn't the only reason<sup>[32]</sup>. Toxins, medications, or other problems may cause osteomalacia if they lead to vitamin D malabsorption. Since osteomalacia occurs with frequency in many gastrointestinal (GI) illnesses, a precise count is difficult to get. A long-term vitamin D shortage (possibly worsened by a lack of calcium) may raise blood calcium and cause a rise in blood PTH levels in pathophysiological terms.

**Table 1: Vitamin D Causes Osteomalacia deficiency**

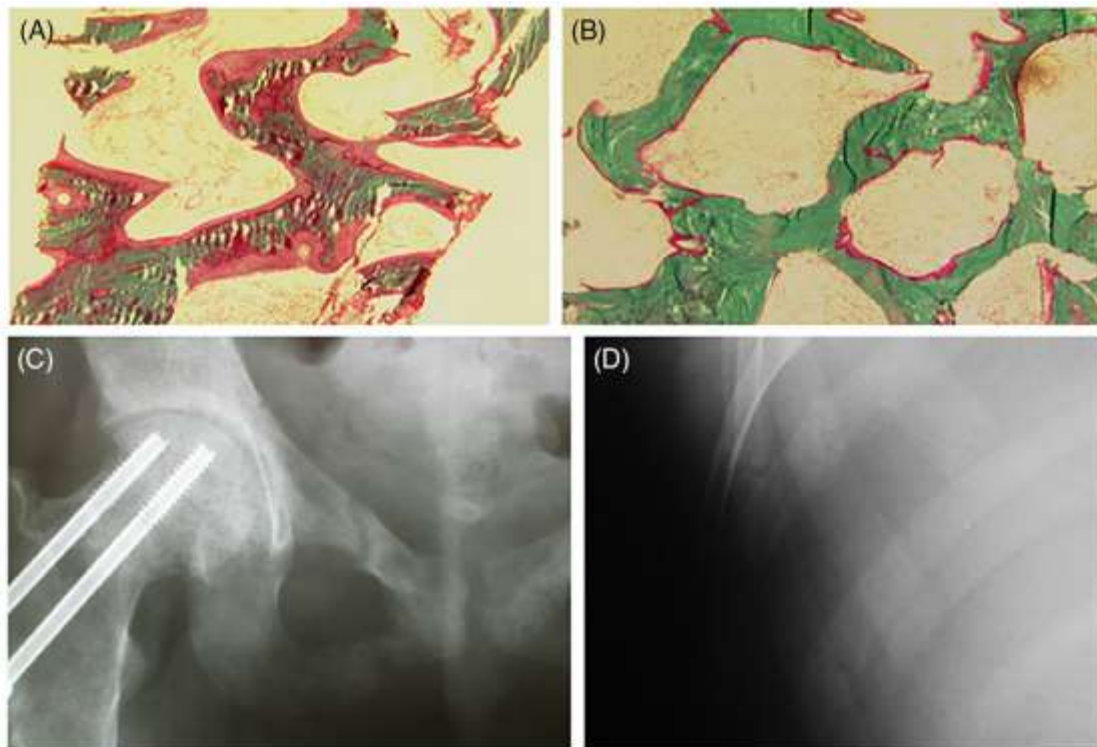
Extrinsic (extraneous to the individual such as environmental, secular or behavioral)
Inadequate dietary intake of vitamin D
Pancreatic insufficiency including cystic fibrosis (uncommon)
Advancing age with decreased cutaneous production of vitamin D
Fully covered garbs (veil, hijab, burqa, Indian Saree etc.)
Dark skin pigmentation
Intrinsic (within the individual)
Use of sunscreens (especially >8 SPF)
Morbid Obesity
Malabsorption due to various gastrointestinal disorders
Gastrectomy (partial, total, or gastric-bypass procedures)
Impaired or genetically defective vitamin D-25-hydroxylase
Gluten enteropathy (Celiac sprue)
Primary Biliary Cholangitis (uncommon)
Decreased exposure or avoidance of sunlight
Small intestinal disease, resection or bypass
Immaturity
Neonatal hepatitis
Cirrhosis of the liver
Impaired or genetically defective 25-hydroxylase
Genetic defect (Vitamin D dependent rickets type-1A)
Chronic renal failure "Acquired" vitamin D deficiency
<b>Anticonvulsants</b>
Calcium malabsorption with secondary hyperparathyroidism Primary hyperparathyroidism
Paget's disease of bone (presumed excess consumption in Pagetic bones)

**Osteomalacia's Clinical Signs and Symptoms**

One of the most prevalent, and first, clinical symptoms of osteomalacia is generalised bone pain and soreness, muscular weakness, and fragility fractures. There are a lot of nonspecific skeletal symptoms<sup>[35]</sup>. They are present in bone and non-bone disorders. Incomplete mineralization means that there is less of a mineral lattice throughout the bone, and hence less structural support. As a consequence, the long bones of the lower extremities bend somewhat. This study has

shown that deficient mineralization of rachitic mouse fibrils is associated with increased extensibility and reduced stiffness<sup>[36-37]</sup>, thereby offering higher flexibility and elongation. Finally, due of a lower mineral content and bone strength, it is possible for fractures to develop in both the axial and appendicular skeleton. In many cases, pseudofractures are seen in osteomalacia and in the correct clinical situation, this finding is considered diagnostic of the disease.





**Figure 2: Bone histomorphometry in an osteomalacia patient. Before therapy (A), there is widespread and extensive osteoid, and after therapy with vitamin D, there is practically total eradication of osteoid (B) A patient with celiac disease-related osteomalacia. (C); two ribs' transverse lucencies (D). Celiac disease was ultimately discovered in the patient.**

On the clinical level, patients often complain of proximal muscular weakness, with the most frequent manifestation being weakness in the thighs and knees. Additionally, they often have a distinct waddling stride due to their inability to raise their extremities off the ground. Even when muscular weakening is severe, there are some situations in which movement is almost impossible<sup>[38]</sup>. Sometimes the patient is confined to a bed to resemble a state of paralysis. The difficulty in establishing the existence of vitamin D insufficiency and osteomalacia is that muscle symptoms may be subtle and worsen over many years, requiring several visits to the doctor to help identify the issue. Clinicians who visit patients who have bone and mineral disorders can request help from medical specialists, such as rheumatologists, orthopedists, and neurologists, prior to seeing a bone and mineral expert<sup>[39]</sup>. Although the clinical importance of vitamin D insufficiency as a sign of muscle problems is well recognised, the root cause of muscular manifestations remains unclear. While the proportional contributions of hypocalcemia, hypophosphatemia, and increased PTH levels to the development of rickets and osteomalacia are not well known, it may be assumed that the hypocalcemia and hypophosphatemia is greater. Rickets and osteomalacia may both occur in the absence of high amounts of PTH but may also occur with insufficient amounts of vitamin D<sup>[40-41]</sup>. osteomalacia is a condition that is sometimes

found to be related with several disorders not all of the illnesses which have been associated to vitamin D deficiency, osteomalacia, and other health problems have been discovered because of these three reasons: vitamin D deficiency, osteomalacia, and the fact that the status of each condition is unknown: i) there is no histological documentation to ascertain the disease's prevalence, (ii) a misdiagnosis of osteoporosis is made due to the fact that the more prevalent metabolic bone disease—osteomalacia, and (iii) most healthcare providers and specialists are unaware of the disease. In the part to follow, we will be discussing the most essential of these clinical problems, with a focus on the pertinent components in relation to the subject of this essay.

Bariatric surgery has been shown to be an effective long-term weight management strategy, as well as a helpful tool for treating many medical disorders. In general, the most widely utilised methods for the sleeve gastrectomy and the Roux-en-Y gastric bypass are sleeve gastrectomy and the Roux-en-Y gastric bypass. More specifically, both operations, but mainly the latter, lead to vitamin D malabsorption, which causes osteomalacia if this happens over an extended period of time<sup>[42]</sup>. It is, therefore, in accordance with the American Society for Metabolic and Bariatric Surgery recommendations to supplement with vitamin D in varying dosages. There are just a few research investigating histological

osteomalacia in these individuals, and unfortunately, most of them discovered that the disease had little effect on their bones. Research conducted out in obese people who had biliopancreatic diversion with duodenal switch before and after surgery indicated that increased osteoid volume and reduced cortical thickness were seen in the subjects four years after the operation. It is also vital to bear in mind that following bariatric surgery, vitamin D is poorly absorbed.

#### **Antiepileptic Drug**

While a number of earlier studies have shown osteomalacia in adults with epilepsy, we do not yet know if it also occurs in children with epilepsy. Additional points to consider in interpreting these results include the following: Many of these studies were conducted in a medical environment where a confounder may have existed<sup>[43]</sup>. It follows that the proportional significance of vitamin D insufficiency to the pathogenesis as well as other facets below is unknown. Osteomalacia was determined to be the result of cytochrome p450 liver enzyme-inducer antiepileptic medications<sup>[44-45]</sup>. It is possible that poor nutrition and limited exposure to sunlight were contributing factors, but other contributing factors include prescription medications with known anticonvulsant effects. Phenobarbital upregulates the expression of 25-hydroxyvitamin D(3)-24 hydroxylase gene in vitro. The data presented on the study done on institutionalised patients who had a fracture in the last year showed that trabecular bone resorption was greater in patients than in control individuals<sup>[46]</sup>. The high mineralization rate led to an increase in osteoid. This might indicate osteomalacia. Even while it has not been determined just how prevalent osteomalacia is in individuals on antiepileptic medicines, as well as the association between vitamin D insufficiency and new antiepileptic treatments, it seems that people are being encouraged to supplement their diet with vitamin D.

#### **Methods of Action**

Although they seem to be based on a combination of events, the methods of action of analogues with increased ant proliferative, prodifferentiating, and lower calcimimal side effects are not completely understood. It might be related to pharmacokinetic variations that cause analogues to have lower calcemic effect. DBP has a half-life of roughly 6 hours because it is 500 times less susceptible to the action of Maxacalcitol<sup>[51-52]</sup>. On the other hand, Eldecalcitol has four times the binding affinity for DBP as 1,25(OH)2D3, resulting in four times the plasma levels of DBP. DBP has three hydrogen bonds that are present in a certain conformation to accept one hydrogen bond from calcitriol. In comparison, the other three hydrogen bonds with the 3-hydroxypropyloxy group of eldecalcitol interact with the DBP molecule in a different orientation, according to a recent study.

As a consequence, the analogue is exposed to the cells for a longer duration. Elde-calcium-titol binds to VDR less strongly than calcitriol and hence has a

lower ability to trigger CYP24A1 mRNA production, but it is significantly more successful in binding VDR and so activating CYP24A1 expression<sup>[53]</sup>. Despite this, it is assumed that eldecalcitol is not digested due to CYP24A1 activity, resulting in a prolonged time of action in the tissues. According to a cohort study, the ability of an analogue to promote contact between VDR and coactivator proteins correlates with its anti proliferative effects and potential for cotranslational protein connection<sup>[54-55]</sup>. By doing research on the crystal structure of VDR's ligand-binding domain, this study has shown the presence of an enlargement of this binding pocket around the location of carbon 2 of the ligand's A-ring. In contrast to the VDR-LBD-1,25(OH)2D3 complex, the LBD in the VDR complexed with a peptide including a coactivator and an LXXLL peptide and with the VDR's ligand binding domain including the carbon 2 analogue 2MD and demonstrated that the LBD linked to 2MD remained unaffected<sup>[56]</sup>. The analogues did not have a major influence on protein conformation when interacting with the LBD, but they did have the ability to impact protein conformation when interacting with 1,25(OH)2D3, according to the results of both studies. After being administered a regimen of 25-OH D3 or its equivalents, researchers undertake ChIP testing to look for VDR protein binding sites across the genome. It compared the number of VDR molecules bound to the CYP24A1 and TRPV6 loci in intestinal tissue after treatment<sup>[57-58]</sup>. It discovered that while both treatments increased the number of VDR molecules bound to these genes in the intestine, the analogue treatment caused a sustained increase in the number of VDR molecules bound to these genes, which increased the degree. Also, while 1,25(OH)2D3 or vitamin D analogues may encourage or decrease minor physical contact variations, such as closer or farther contacts with certain amino acid residuals, this leads to longer permanent interactions with tissue coactivators<sup>[59]</sup>. The same number of coactivator interactions is estimated to be required by 10 times lower dosages of inecalcitol than 1,25(OH)2D3. Structures for VDR-LBD, 20-epi vitamin D analogues, or the LBD-binders for the A-ring and the lateral chain were found to attach all three compounds to the same residue in the LBD and to hold them in place in the A-ring and the lateral chain for hydroxyl groups<sup>[60-61]</sup>. The addition of the Gemini analogue, which has two identical side chains branching at carbon 20, to the GGA synthesis was useful since it provided fresh insight while maintaining or improving VDR binding affinity while considerably increasing transactivation efficacy. The VDR-Gemini complex undergoes a partial inversion in its G I (inverse agonist) and G s (agonist) modes when N-Cor levels become excessive. While there was no change in the overall structure of the LBD, the inclusion of a ligand with a 25% increase in volume had no influence on the arrangement of the LBD ligands<sup>[62-63]</sup>. To increase the biological potency of the original Gemini analogue, many derivatives (two separate side

chains) were created, were analysed to see whether they interact with the zebrafish zVDR- LBD. The extra cavity generated by the additional side chains in the LBD matches the original Gemini. According to these structures, the fluorine atoms connected to the side chains are required to stabilise helix H12, allowing for greater interactions with coactivator proteins.

#### IV. RESULTS

This analysis investigated the features of the 87 SNPs that had been genotyped in the SLSJ case. The CD86 SNP failed the test design, situated in the CD86 gene, whereas the GC SNP passed the test design, which is located in the GC gene. The SNPs do not function as singleton markers, indicating that they tag other SNPs in the genes. There was just one gene that had the CYP27B1 variant. Further study revealed that the non-random distribution of the minor allele frequency was found in the HapMap sample, and the non-random distribution was seen in the SLSJ research. The two groups had a variance of about 2%. 16% of SNPs rs4308217, found in the CD86 gene, had the highest volatility<sup>[65]</sup>. This single SNP in the CYP24A1 gene has been found to be an individual and has thus been removed from further investigation.

FBAT association testing results in a higher incidence of osteomalacia when modest p values (in the range of 0.10) are present. The p value for osteomalacia is less than 0.1 for individuals who have it. All five SNPs found in the IL-10 gene are located in the promoter (rs1800871, rs1800872, and rs1800896), in the first intron, and in the 3' region. Only three of them were found to be in extremely close proximity ( $r^2$  equal to or lower than 0.99), while the others ranged from a small distance apart to moderately apart. When using HapLOF for the three highly linked SNPs, it was discovered that two haplotypes were present at an allele frequency of more than 1 percent in the SLSJ population<sup>[66]</sup>. These two intronic SNPs have been linked with a word which implies an allergy or hypersensitivity to specific environmental substances, and their genetic association was shown to be in moderate linkage disequilibrium. Osteomalacia may be due to three intronic SNPs in the CYP24A1 gene. The third SNP showed no linkage disequilibrium with the previous SNPs. Additionally, it should be noted that the promoter region of the CD86 gene showed an association with osteomalacia. There were additional associations between this SNP's trends and osteomalacia.

##### *Role of Vitamin D deficiency in hypertension*

As per the American general of clinical nutrition 73% to 90% of people are suffering from Vit D deficiency and that is the major cause of osteomalacia and hypertension.

Hypertension, often known as high blood pressure, is one of the world's most common and deadly diseases<sup>[67]</sup>. Hypertension is caused by a number of risk

factors, including age, race, tobacco use, high salt intake, and so on. Low vitamin D levels are one of the risk factors we'd like to highlight. While there is solid evidence that Vitamin D is crucial for bone and muscle function, its involvement in hypertension has been the subject of recent controversy. Many studies, however, have found an indirect link between 25-hydroxyvitamin D serum levels and blood pressure.

A 2013 study looked at a number of reviews that included people with hypertension. They discovered that every 10 ng/ml increase in Vitamin D levels resulted in a 12 percent lower risk of developing hypertension<sup>[68]</sup>. When compared to the general population with the lowest levels of Vitamin D, those with the highest levels had a 30 percent lower risk of getting hypertension.

##### *Role of Vitamin D deficiency In Diabetes*

Vitamin D deficiency is a common problem in persons with and without diabetes all over the world. As revealed in this 2011 study Trusted Source from Canada, research has repeatedly found a clear link between low vitamin D levels in people with insulin resistance and a high risk of developing type 2 diabetes.

"This latest study appears to suggest that supplementation before or shortly after diagnosis preserves the body's ability to respond better on the cell level to insulin, counteracting the characteristic of type 2 diabetes - insulin resistance," Jennifer Smith, CDE, RD, told Healthline.

The other thing it appears to help with is helping the beta cells in the pancreas that create insulin to be healthy and functional, said Smith<sup>[69-70]</sup>, who works at Integrated Diabetes Services and treats patients with different types of diabetes all around the world.

Insulin secretion is controlled by beta cells. According to a 2016 study published in Diabetes Care Trusted Source, gradual beta cell failure is the leading cause of type 2 diabetes in about 60% of those diagnosed.

The other 40%, on the other hand, may be able to reverse the illness by making considerable adjustments to their diet, exercise, and body weight. "As type 2 diabetes progresses, patients will typically need to begin using insulin due to a steady depletion of beta cells. This implies that oral diabetes treatments that induce the body to create more insulin are no longer effective, necessitating insulin injections."

Despite the study's excellent findings on insulin sensitivity and production, there was minimal difference in fasting glucose levels and HbA1c levels between the placebo and control groups.

#### V. CONCLUSION

As a result of several research papers, report positive benefits of 1,25(OH)2D3 on reducing the malignant behaviour of cancer cells. It has been shown that vitamin D signalling mostly impacts cancer progression; however, most research analyzing preclinical in vivo models of cancer seems to indicate



that it only influences the process of cancer growth<sup>[71-72]</sup>. Contrary to this, in keeping with the latest meta-analyses of observational research and randomized clinical trials, the results of vitamin D status studies suggest that there is a positive association between vitamin D status and mortality, but not with cancer incidence.

Osteomalacia is an emerging public health problem, and so there is a need for improved knowledge of its epidemiology in both industrialised and developing nations. All practitioners, regardless of specialty, should be made aware of the metabolic bone disease and the many treatments and medications available<sup>[73-74]</sup>. It is vital to remember and be thankful for, particularly among the elderly, that a loss in Bone Mineral Density (BMD) does not mean an occurrence of osteoporosis. Osteomalacia is a disorder that develops in people with an increased chance of getting this illness, and hence it is very important to carry out bone biopsy examinations on such people<sup>[75]</sup>. These illnesses, for example, are the same as those that might cause osteomalacia and not react to vitamin D therapy, certain hypophosphatemic disorders, and to determine whether the skeletal health of patients with renal failure is appropriate, you should do a complete medical exam. Due to the inherent difficulties in conducting bone biopsy procedures in clinical practise, a simple instrument that would assist physicians in the diagnosis of osteomalacia should be created to aid in its diagnosis, as suggested by the Japanese societies. However, this particular score should have international validation, given that there is a bone histology diagnosis of osteomalacia that occurred simultaneously.

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