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Physiology Of Calcitriol, Its Role In Body Functions And Highlights About Immunological And Thyroid Activities: A Molecular View On Vitamin D Receptors And Gene Polymorphism.

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ABSTRACT

Vitamin D is a secosteroid hormone, which is attracting the attention of the scientists for its therapeutic functions. As it is playing the pleotropic role in multiple physiological process, the deficiency of vitamin D is considered as the major health issue. The main reason for the deficiency of vitamin D is lack of exposure to the sunlight. The vitamin D receptor is a member of steroid hormone super family. Recently the highlighting issues are the action of vitamin D in non-skeletal tissues, cardiovascular, diabetes mellitus, cancer. currently, there is a need to increase the vitamin D status in individuals worldwide as it has been shown to improve the auto immune and infectious disease, type-2 diabetes mellitus, neurocognitive disorders. This review is elucidating the central role of vitamin D in maintaining the overall health. Highlights about vitamin D receptors and a molecular view on vitamin D receptor gene polymorphism.
Keywords: Vitamin D, steroid hormone, gene polymorphism.

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INTRODUCTION

Recently, for all the researcher's vitamin D has become the prime subject of interest, because of the widespread arms of vitamin D in living system. Current research evidences that, the world is suffering from the vitamin D insufficiency and deficiency pandemic.

Vitamin D deficiency is a risk factor for human being right from the infancy and throughout the life[1]. The reason behind this deficiency is lack of consumption and exposure to sunlight due to scheduled work. About one billion people are suffering from vitamin D insufficiency and deficiency[2]. The traditional name for vitamin D is Sunshine vitamin. But in late 20th century vitamin D is considered as conditional vitamin D. India is a tropical country and the people of India gets ampule of sunlight throughout the year. But still hypovitaminosis is more common in India[3,4].

Vitamin D is a secosteroidal hormone precursor, which encompasses several compounds. The two major isoforms are ergocalciferol (vitamin D2) which is available in plants and cholecalciferol (vitamin D3) is synthesized at the skin level from 7- dehydrocholesterol after exposure to ultraviolet B (UVB) radiation[5,6]. These vitamin D isoforms will be transported to the liver, where Vitamin D gets hydrolysed at 25th position by 25 hydroxylase enzymes to 25 hydroxy vitamin D2 (25(OH)D2) and D3 (25(OH)D3). These are the two main circulating isoforms of vitamin D and reflects the vitamin D status [5,7]. Vitamin D3 is the most considering isoforms in humans[8].

25 hydroxy vitamin D (25 (OH) D is the major circulating and stored form of vitamin D. Among 1,25 (OH)2 D and 25 (OH) D, 25 (OH) D is considered as the best marker to measure the whole-body vitamin D status[9,10,11]. Because 1,25 (OH)2 D has short half life about 4-6 hours, but 25 (OH) D has half-life about 14 days.

At physiological concentration, 25(OH)D3 is inactive and need to be activated to 1,25 dihydroxy vitamin D3 (1,25 (OH)2 D3). Which is achieved by 1α- hydroxylase enzyme in the kidneys (encoded by CYP27B1). 1α- hydroxylase enzyme activity is regulated by parathyroid hormone (PTH) levels, high levels of 1,25 (OH)2 D3 levels and fibroblast growth factor 23 (FGF23) exerts negative feedback. 1α- hydroxylase expressed in extra renal sites like bone, skin, colon, brain and immune cells doesn't have regulation by parathyroid hormone (PTH). The 25(OH) D and 1,25 (OH) D3 will be inactivated by 24- hydroxylase. Although arguable vitamin D status the deficiency is labelled as 25 (OH) D level < 50 nmol/L, insufficiency is 50-75 nmol/L of 25 (OH)D[5,6,12].

Vitamin D exerts its genomic action through vitamin D receptor protein (VDR) which is a member of nuclear hormone receptor super family. It modulates the transcription of target genes by complexing with vitamin D responsive elements (VDRES) in the promoter region of target genes[13].

The key hormone in the regulation of the musculoskeletal homeostasis is considered to be 1, 25 (OH)2 D3. After discovering the presence of vitamin D receptor in many tissue types it has been shown more interest in extra skeletal effects of 1,25 (OH)2 D.[14,15]

The physiological effect of vitamin D contributes to the development, protection, transmission, and plasticity role on the vascular endothelium and improves insulin sensitivity.[16-19] These evidences that vitamin D as a biomarker of general health and deficiency of vitamin D has been correlated to the presence of metabolic syndrome, cardiovascular disease, cancers, infections, neuromuscular disorders.[20-22]

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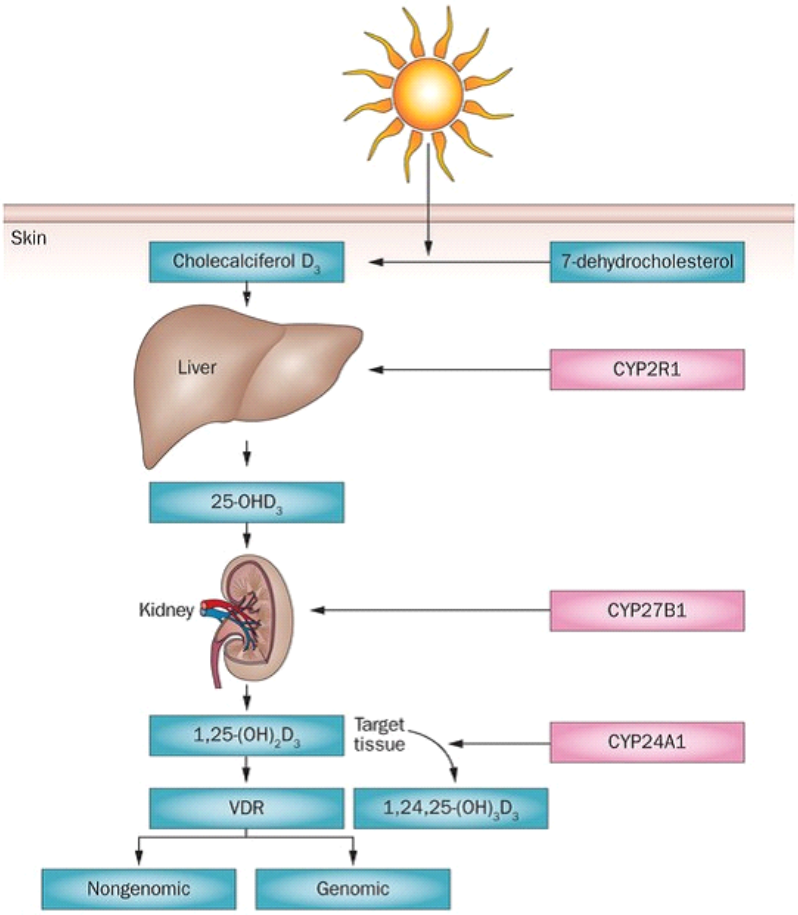

Figure 1: Synthesis Of Vitamin D

Role of Calcitriol in the following:

Calcium

Vitamin D exerts it effects in increasing absorption across the intestinal epithelial cells. Because of the widespread of 1,25 (OH)2 D receptor throughout the intestine, calcium absorption takes place throughout the small intestine. But the efficiency of absorption is highest in duodenum.[23]

Based on the dietary load of calcium, serum concentration of 1,25 (OH)2 D and bioavailability of dietary calcium, the net absorption of calcium varies.[24] In the stomach acidification solubilizes calcium and in conditions like achlorhydria, calcium absorption is decreased.[25] In physiological conditions, as the age advances the ability of the intestine to absorb the calcium will be decreased. And this may be the reason behind the pathogenesis of osteoporosis.[26]

Bone

For normal condition bone growth and maintenance of skeleton, vitamin D is needed. Calcitriol has duel effect on bone

- Stimulates osteoclastogenesis, bone resorption
- Modify osteoblast function and bone mineralization

Studies showed that in humans excess 1,25 (OH)2D enhances oteoclastogenesis and borne resorption. Vitamin D deficiency impairs bone mineralization and osteoblast activity.[24] The coordinated actions of calcium and 1,25 (OH)2 D with VDR is required for growth plate development. Calcitriol regulates

osteoclastogenesis by reciprocal regulation of receptor activation of NF- kB ligand (RANKL) and osteoprotegerin (OPG) expression of RANKL on the surface of osteoblasts is increased by VDR.[27]
Deficiency of vitamin D causes secondary hyper parathyroidism, resulting in decreased level of phosphorous and calcium. Phosphorous should be adequate for bone mineralization. Low serum calcium and phosphorous concentration causes defect in bone mineralization, which leads to rickets in children and osteomalacia in adults.

Kidney

Activation and metabolism of vitamin D takes place in kidney. Kidney plays a major role in reabsorption of calcium and phosphate. 1α hydroxylation of 25 (OH) D takes place at proximal tubule of kidney. In chronic renal failure the activity of 1 α hydroxylase is reduced, which leads to renal osteodystrophy. Calcitriol increases the distal tubular reabsorption of calcium.[24] Calcitriol enhances reabsorption of phosphate in proximal tubules of kidneys, which maintains the phosphate homeostasis. But the calcitriol, parathyroid hormone and FGF-23 complex will reduce reabsorption of renal phosphate.

Skin

The ability of calcitriol to inhibit the proliferation and immune activity suppression have been used for the treatment of psoriasis, a disorder of hyper proliferative abnormal differentiation.[37] Newtons- Bishop et al stated that on supplementation of calcitriol, there is a decrease in risk of recurrence of melanoma compared to those who are not treated with vitamin D.

Cancer

Calcitriol has influential role in preventing progression of cancer by reducing cell proliferation, promoting cell differentiation, apoptosis of cancer cells, reducing angiogenesis, inflammation and metastasis.[28] 1,25(OH) 2 D inhibit tumour growth factor (TGF), which stimulates proliferation of tumour cells. Cancerous cell cycle progression at G1- G0 transition will be prevented by vitamin D and vitamin D receptor, which leads to reduce the rate of cell proliferation.[29]

Cardiovascular disease

Many prospective studies states, there is an inverse relation with vitamin D levels and cardiovascular disease. Vitamin D could impact cardiovascular events, either by VDR in smooth muscle, vascular or cardiac muscle or indirectly by promoting calcium absorption at the expense of lipid absorption or excretion in gut.

As shown in various epidemiological studies there is also an association between vitamin D and hypertension. On vitamin D supplementation or expose to UV radiation, there will be an increase 25(OH) D levels by increasing RAS activity which in turn have antihypertensive effects.[29]

Diabetes mellitus

Calcitriol having immunomodulatory activity, implicated in prevention of type 1 and type 2 diabetes mellitus, by reducing cytokine production, proliferation of lymphocytes and distribution of beta cells of pancreas. B cells of Langerhans express VDR and vitamin D results in insulin resistance[30]. 25 (OH) D will be low in obese people, and those are more prone to get diabetes and metabolic syndrome. Calcitriol promotes lipogenesis while lipolysis is decreased and VDR is expressed in adipocytes.[31] As shown in the observational study improving the status of vitamin D leads to increased insulin sensitivity. Children on vitamin D supplements have 30% reduction in risk of type 1 diabetes.[32]

Immune function

It is essential to regulate the immune system by vitamin D for protecting against infectious diseases. VDR present in macrophages, dendritic cells, β cells and T cells, which regulates both innate and adoptive immunity. Vitamin D is capable of stimulating an antimicrobial peptide called cathalicidin, while exposure to foreign antigens. These cathalicidin plays a key role in innate difference mechanism and regulates the transcription of VDR gene.[33]

By modulating the functions of dendritic cells, the adoptive immune response will be governed by calcitriol. It inhibits maturation of dendritic cells and generates synchronised action by expression of cytokinin [IL-1, IL-2, IL- 12, IL- 17, IFN- γ] on T cells. The global effects of these immune modulating actions are thus a down regulation of acquired immune system (8). The proliferation of T lymphocyte is also inhibited and expression of TH-1 is shifted to TH-2.[34]

Immunological subsystem that includes the cells and mechanisms implicated in the first line defence from infections are called innate immunity. In antimicrobial response the expression of VDR increases when monocytes are exposed to different pathogens.[35] Most highly specific immune response for each pathogenic antigen is an adoptive immunity and is mediated by B and T lymphocytes. The immune modulatory effect of the vitamin D, downregulates the monocyte expression of the proinflammatory cytokines, including tumour necrosis factor- α (TNF- α) and interleukins-6 (IL-6). These are involved in the inflammatory pathway that leads to B and T lymphocytes activation and proliferation.[36]

Vitamin D receptors

Maestro et al. (2016) reported that the vitamin D receptor (VDR) is found in most human tissues and more than 1000 target genes.[38] Calcitriol exerts its effects with the help of high affinity VDR through a series of cell signalling or a ligand activated transcription factor.[39,40] The genomic or non-genomic mode of action can be executed using n-VDR, or m- VDR respectively.[41,42] In the cell, binding to the membrane receptor, calcitriol exerts non-genomic effects by initiating multiple signals which results in immediate response in the target cells. The genomic effects of the calcitriol through nuclear receptor binds to target gens and leads to gene expression.[43]

Types of vitamin D receptors (VDR)

Nuclear Vitamin D receptor (n-VDR)

Vitamin D receptor is not only limited to the classic target tissues of vitamin D but it is widely distributed. vitamin D receptor belongs to the nuclear receptor superfamily. By regulating the expression of genes that mediate biological activity. The nuclear receptor acts as transactivating transcription factor.[44] The vitamin D receptor is encoded by a large gene (>100 kb), which is present on the long arm of chromosome 12q,12 in humans. It composes a complex intron/exon structure and is constitute of 9 exons.[45] The 5' untranslated region encodes the exon 1a to 1f. the translation start site which consists of DNA binding domain is encoded by exon 2 and 3. The region comprised two highly conserved Zink finger motifs. One in each domain is a distinguishing feature of the nuclear receptors. The overlapping ligand binding domain is encoded by exon 4 to 9, which is a strong heterodimerization domain. Exon 9 localizes at the 3' UTR region.[44] In mouse the VDR gene is located on chromosome 15.[46]

The Zink finger motif which is present in DNA binding of the VDR is the core of the VDR protein, involved in the activation of the target genes. When calcitriol binds to the receptor, two independent protein interaction surface form on the VDR protein, of which the first one is needed for specific DNA binding and the second one recruits the large coregulatory complexes, which is necessary for gene modification.[47]

Eventually the VDR forms a heterodimer with the retinoid X factors (RXR). This heterodimer recognises the vitamin D response element (VDRE) located in the promoter of target genes of vitamin D. The calciferol binds to the C terminal region of the receptor, which is located in the 12 helical LBD.[48] The target gene translational activity is to activate (co-activators) or inhibit (co- repressor) the coregulator protein complexes with calcitriol. Protein like the vitamin D receptor interaction protein complex (DRIP) is also known as VDRE at the transcription start site (TSS).[49] Proteins such as the steroid receptor coactivator family 1-3 (SRC 1-3) helps in trans activation.[50] Genes get transcribed leading to the formation of respective proteins like SLUG, which may downregulate genetic functions by VDR.[51] The vitamin D target genes respond in a cell specific manner. It has been invented that the total number of vitamin D targets in the human genome is more than one thousand. This is further supported in cells such as human lymphoblastoid and THP-1 human monocytic leukaemia cells used for chromatin immunoprecipitation combined with high throughput sequencing (CHIP- SEQ).[52,53]

The nuclear VDR – calcitriol complex has a classic genomic ligand pocket called the VDR genomic pocket (VDR- GP), shown by the X- ray crystallography.[54] VDR- GP favours a bowl like molecular geometry with calcitriol by X ray and computational studies, downregulated by Rochel et al. (2000).[55] Frequent polymorphisms are seen in n-VDR gene. Polymorphism can be defined as sequence variations transpiring in a population and are detected using technique like restriction fragment length polymorphism (RFLP). Polymorphisms alter the gene expression, thereby affecting protein levels of the VDR gene, leading to functional changes.[56,57]

Membrane VDR (m- VDR)

The interaction of calcitriol ligand with specific binding sites on the plasma membrane and vesical membranes of target cells referred to as membrane VDR (m-VDRs), which affects the non-genomic activity. The m-VDRs are also known as 1,25 membrane associated rapid response steroid binding proteins (1,25 MARRS), Protein disulphide isomerase family 3 (PDIA-3), a member 3 endoplasmic reticulum proteins 57 and 60 (ERP 57, ERP 60) and glucose regulated protein 58 (GRP-58). [58,59] These are the chaperone proteins and coupled to signal transduction system.[58]

The association of 1,25 MARRS with membrane scaffold proteins like caveolin that are associated with lipid rich craters of the plasma membrane and are responsible for the formation of caveolae in multiple cell types.[60] On the plasma membrane and other membranes of the cell organelle the flask shaped invaginations are found, which is none other than caveolae. The main components of which are cholesterol sphingolipids and the protein caveolin.[61] Caveolin exists in 3 isoforms, caveolin 1,2 and 3, which is according to their location and function in different cells. The primary function of caveolin was thought to be vesicle trafficking. But they also take part in cholesterol biosynthesis, signal transduction, tumour suppression and anti-proliferative action.[62]

Auto immune thyroid disease

The most frequent autoimmune disease is auto immune thyroid disease (AITD), with an estimated prevalence of 5%. Especially in the female population progressive increase in incidence is seen. The autoimmune thyroid disease is seen in more in adult women than in adult men. The abnormal thyroid function ratio in male to female is 1-2%/7-9%.[63]

An organ specific deregulation of the immune system resulting in the T-cell mediated autoimmune disorders which is called AITD. The mechanism involved in this autoimmune response has not been elucidated completely through the prediction in genetic involvement, even the environmental factors has been demonstrated to trigger the autoimmune process.[64] Vitamin D plays a major role in auto immune thyroid disease through its enhancing effects on the innate immune system and inhibitory actions on the adoptive immune response.[65]

Some preclinical and clinical studies found an association between AITD and vitamin D deficiency.[66,67] McDonnell described an interesting homology between the VDR and the thyroid hormone receptor.[68] Five years later, Berg et al. demonstrated the VDR expression on follicular thyroid cells.[69] However, VDR and the thyroid hormone receptor share partners for heterodimerization.[70] Furnier et al. investigated the effect of a combined treatment with cyclosporine A and calcitriol using an experimental model of AITD in mice.[71]

The most common organ specific autoimmune thyroid disorders are Hashimoto's Thyroiditis and Grave's Disorder.[72]The combination of genetic predisposition, environmental factors influence the lymphatic infiltration in to the thyroid gland and production of thyroid specific antibodies. This condition is called auto immune thyroiditis (AITD).[72,73]

Hashimoto's Thyroiditis, a chronic autoimmune thyroiditis, is a typical T- cell mediated autoimmune disease, where the antithyroid Peroxidase (anti-TPO) and/ or anti thyroglobulin (anti TG) antibodies are present in serum, which diffuse goitre. The thyroid hypofunction and intra thyroidal infiltration of B and T lymphocytes with CD4+ Type 1 T helper cells (Th-1) subtype predominance.

In Grave's disease (GD) CD4+ type T helper (Th-2) cells, will induce the production of antibodies to bind the thyroid stimulating hormone (TSH) receptor, where lymphocytic infiltration is mild. Here the

stimulation takes place for the growth and function of thyroid follicular cells, leading to hyperthyroidism indicating a humoral immune response.[72]

Types of autoimmune disorders

Hashimoto's thyroiditis

T cell mediated autoimmune disease characterized by goitre is represented by Hashimoto's thyroiditis. In this condition presence of circulating anti thyroid peroxidase (anti TPO) and / or anti thyroglobulin (anti TG) antibodies and infiltration of intra thyroidal B and T cells with CD4+ T helper 1 takes place and the degree of hypo function of thyroid gland depends on this alteration.[64,74]

Previous studies observed that low level of vitamin D and the risk of HT onset seems to be closely associated. However, patients with HT has higher proportion of hypovitaminosis D (over 60%). Moreover, vitamin D deficiency (< 20 ng/mL) has more association with HT, that vitamin D insufficiency (21-29 ng/mL).[75-78]

The association between vitamin D and HT was published in 2009. This was the first observational study. A community-based survey on 642 adults to investigate the relationship between serum vitamin D concentration and thyroid autoimmunity was conducted by Goswami et al. and they found a significant inverse association between calcitriol and TPO antibody.[79]

In paediatric population, Comurdan et al. observed the inverse association between calcitriol levels and TPO antibody titre.[80] A strong negative association between serum vitamin D concentration and TSH levels were demonstrated by Mackawy and co-workers. In the clinical condition vitamin D deficiency in HT patients who develop hypothyroidism has TSH value more than 5 mIU/L.[81] Simsek et al. done a prospective study with 82 HT patients and they divided the samples in to two categories. And supplied the cholecalciferol 1000 IU/day for one month. And the other group is devoid of this supplement. The result showed drastic decrease in the level of TPO antibody and TG antibody in the sample group who underwent the supplementation.[82] Other prospective study has proved that supplementation of cholecalciferol was related to decrease in TPO antibody and TG antibody levels both in vitamin D insufficiency and deficiency.[83-85] It is also been proposed that an increase of 5 ng/ml. of vitamin D level was correlated to a significance of 20% in the risk of HT.[86]

The influence of vitamin D supplementary treatment on thyroid function and thyroid auto antibody levels were conducted on 11,017 subjects by Mirhosseini et al. in 2017. They found 30% decreased risk of hypothyroidism onset in ≥ 50 ng/ml of serum 25 (OH) D3 levels, 32% decreased risk of increased thyroid auto antibodies level. They concluded that vitamin D supplementation provide protection from new onset of thyroid disease during a 12 month follow up.[87] The study by Chahardoli et al. presented a significant decrease in TSH levels after weekly supplementation with 50,000 IU of cholecalciferol.[88]

In contraction to the above investigations, few studies however failed to document association between vitamin D deficiency and a higher prevalence of HT.[89,90] Few studies raised the questions on the preventive role of vitamin D in AITD. Further investigations are needed to evaluate the preventive and therapeutic effects of vitamin D in AITD.

VDR polymorphism is a booster evidence to evaluate the increased incidence of HT.[91] The most frequent polymorphism includes FokI, BsmI, Taq I and ApaI polymorphism. Taq I polymorphism is located in exon- 2 of the VDR gene, a truncated VDR proteins are produced by alteration in the start codon.[92] BsmI and ApaI polymorphism located in intron 8 of the VDR gene, leads to an altered m-RNA stability. A change in intronic sequence affecting the gene expression.[92,93] The FokI polymorphism located on exon 9 and able to alter the stability of m- RNA.[92, 93] Serum vitamin D concentration is influenced by the FokI and ApaI polymorphism. IFN-γ production by monocytes were interfered by BsmI polymorphism and VDR expression influenced by Taq I. In meta-analysis on 8 studies showed that VDR, BSMI and Taq I polymorphism were associated with HT risk.[94] The CC genotype for the FokI polymorphism was frequent in patients with HT was studied by Inoue and co-workers.[95] 11 studies on Asian and Caucasian population included in meta-analysis and observed that the FokI polymorphism of VDR was related with higher risk of HT only in Asian subjects.[96]

Grave's disease

Most common cause for hyperthyroidism in developed countries is grave's disease, which affects mostly women with annual incidence of 14 cases in 100,000 people.[97] The characteristics of grave's disease is presence of TSH receptor autoantibodies (TRAB), which leads to hyperthyroidism, diffuse toxic goitre and ophthalmopathy.[98] Lymphocytic infiltration is milder in grave's disease than HT. It involves mainly to CD4+ T helper cell 2 (Th-2).[99]

The first observational study revealed that concentration of vitamin D were significantly lower in patients without remission of GD compared to the subject with remission.[100] Some prospective study observed that the association between low vitamin D concentration and increased thyroid gland volume in women with newly onset of GD.[101] Prevalence of vitamin D insufficiency was higher in GD patients compared to controls. It was a cross sectional study which included 776 AITD patients by Kim et al.[102] The association between vitamin D and TRAB has conflict result. Some studies prove that there is no association[103,104], but Zhang et al. found an inverse association between serum vitamin D concentration and TRAB levels.[105]

26 case control cohort studies were included in meta-analysis by Xu- and co workers and they found vitamin D deficiency is more frequent in grave's disease when compared to control group.[106] The treatment for the grave's disease by supplement action of vitamin D has minimal study. However, the study includes 210 GD cases with hypovitaminosis, 60 cases received cholecalciferol (1000-2000 IU/day) and 150 cases did not. The recurrence rate was between 38% vs 49%. Unfortunately, the control group had early onset of the disease.[107]

Many studies showed the relationship between polymorphism of VDR gene and GD onset risk, but results are not conclusive. Zhou et al. conducted a meta-analysis in 2009 to compare the association of vitamin D receptor FokI, BsmI, Taq I ApaI polymorphism in grave's disease. But the result showed that in Asian population VDR polymorphism with higher risk of grave's disease, whereas in Caucasian population there is no association.[108]

In recent meta-analysis included 8 studies showed that BsmI and TaqI polymorphism has the association with grave's disease, but there is no association of ApaI and FokI polymorphism.[109]

Thyroid cancer

The most frequent endocrine tumour now a days is called to be thyroid cancer. 5,67,000 new cases report annually. This incidence is much higher in women than in men.[110] The thyroid cancers are differentiated in to 3 categories. a) differentiated thyroid cancer (DTC) b) Poorly differentiated thyroid cancer (PDTC) and anaplastic thyroid cancer (ATC).[111] The recognised risk factor for thyroid cancer are thyroid nodules, family history of thyroid neoplasia etc.[112-116]

The immuno modulatory role of vitamin D in tumour associated inflammation has been studied by many scientists. The anti-inflammatory property of vitamin D expresses in different cancer types through the inhibition of prostaglandin synthesis, suppression of P- 38 stress kinase signalling and inhibition of pro inflammatory cytokines production and NF-KB signalling.[117-119] Passler and co-workers showed that calcitriol play an important role in reducing the inflammatory micro environment in DTC.[120]

Conclusion

In conclusion, there are many observational studies, and meta-analysis revealed that there is a relationship between hypovitaminosis and thyroid diseases. The supplementation of cholecalciferol is beneficial in effective treatment for AITD. The interpretations of the studies till date on vitamin D and thyroid abnormality are inconclusive. However, a large multicentre study involved in the estimation of vitamin D receptor protein in serum and comparison with baseline characteristics and vitamin D gene polymorphism may give a satisfactory acceptable result. Which brightens the role of vitamin D in each individual and the disease-causing mechanism.

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