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VITAMIN D, PLEIOTROPIC ACTIONS, IT'S INTERACTIONS WITH VDR AND SIGNIFICANCE IN GASTROINTESTINAL MALIGNANCIES "AN ANALYTICAL REVIEW"

Gastroenterology

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ABSTRACT

Vitamin D with its multipronged pleiotropic effects, has triggered in depth studies to decipher newer pathways and its beneficial effects in a variety of cancers. Vitamin D is a precursor of Calcitriol which is a potent steroid hormone Calcitriol, once it is synthesized in the body by double hydroxylation reaction, it exhibits a variety of effects in the body. Vitamin D receptors re known to be ubiquitous in nature and hence this potent steroid Calcitriol is known to regulate a variety of cellular pathways that are directly or indirectly implicated in the pathogenesis of gastrointestinal cancers and hence forms the basis of pharmacotherapy employing vitamin D in gastro9intestinal cancers and its role in the prognosis. Hypovitaminosis or vitamin D < 20ng/ml is largely studied to increase the risk of orthopaedic fractures due to falls, osteoporosis, cardiovascular diseases, hypertension, diabetes, reduced immunity, obesity, metabolic syndrome and much more. Calcitriol (1,25-dihydroxycholecalciferol) is implicated in the control and regulation of multiple genes that plays an important role in the function and maintenance of gut physiology, oncology and homeostasis. Studies show that calcitriol plays a key role in the maintenance and integrity of epithelial barrier and absorption of calcium, phosphate and defense mechanisms of the hosts to a variety of pathogens. Active form of Vitamin D also called as Calcitriol, is known to control a variety of inflammatory pathways and responses exhibited by the several secretory and immune cells. Research is still ongoing to establish the prominent role of vitamin D in cancer pathology, Till date the result of several studies including Randomized controlled trials are inconclusive, yet there are many other corelated studies which are in strong support wherein hypovitaminosis D is implicated in the pathogenesis and risks involved in the development of cancer. Vitamin D deficiency is a global problem and supplementation of vitamin D is an economical way to cut down the risk of variety of pathogenetic conditions including risk of cancer of the gastrointestinal tract. In this review, we aim to highlight the beneficial role of vitamin D (Calcitriol) in the pathophysiology and onco-therapeutics of Gastrointestinal malignancies.

KEYWORDS

Calcitriol, Vitamin D, Gastrointestinal Malignancy, VDR, Pleiotropic effects.

INTRODUCTION

Vitamin D is a dynamic seco-steroid that is implicated in variety of physiological responses in the human body and hence considered important in regulating a variety of physiological functions and maintain body homeostasis.[1] Vitamin D receptors are found in almost every tissue of the body and hence are considered ubiquitous in nature, studies carried out in the past have concluded the ubiquitous nature of vitamin D receptors, large scale interest has creeped in the minds of many researchers to decipher the role of vitamin D in various pathophysiological conditions in humans. It's a known conclusion from many studies that vitamin D exhibits multipronged pleiotropic effects in various disease conditions like carcinomas of the breast, prostate, and gastrointestinal malignancies, more so in colorectal cancers as well. It's beneficial role in cardiovascular, metabolic, endocrine, autoimmune, and other chronic inflammatory pathologies are studied to a larger extent.[1]

Many studies in the past have demonstrated the role of vitamin D on cellular proliferation, differentiation, angiogenesis and apoptosis which is extensively studied in many ongoing clinical trials to look into the benefits of vitamin D supplementation in conditions involving these pathogenetic mechanism. vitamin D in many studies have demonstrated it's efficacy as an immune regulatory hormone with its add on benefit of possessing anti-inflammatory properties which mediated by helper T cells (Th1) and this property is found to possess beneficial effect in chronic inflammatory conditions like Multiple Sclerosis, diabetes, psoriasis, psoriatic arthritis and other gastrointestinal malignancies.[2] It is an interesting observation from many trials in the past that vitamin D deficiency in an individual is associated astonishingly with increased cancer risk of breast, colon and carcinoma of the prostate, hence it was concluded from lots of ongoing trials that vitamin D deficiency or deficiency of VDR increases the preponderance of tumorigenesis in humans.[3]

Vitamin D highlights and historical background

Vitamin D, which is also referred to as "Calciferol" or the sunshine vitamin, belongs to the fat-soluble category of vitamins that is naturally present in certain food items and in few other they are fortified and is also available as a supplement for therapy. It is produced endogenously when ultraviolet rays (UV) rays from sunlight gets incident on the skin "the concept of zenith angle", which then triggers the synthesis of vitamin D in the body.[4] The activation of vitamin D that is obtained by various sources has to undergo two hydroxylation reactions in the body for its activation and subsequent action.[4] The first hydroxylation that occurs in the liver converts vitamin D to 25-hydroxy vitamin D which is popularly called as Calcidiol. The second hydroxylation occurs in the kidneys which converts Calcidiol to its physiologically active form called as Calcitriol or 1,25 Di-hydroxy cholecalciferol.[4,5]

Role of VDR and Vitamin D in GIST (Gastrointestinal Stromal Tumors)

Vitamin D plays an important part in maintaining bone health and mineralization. It regulates the body levels of calcium which then regulates the rate of bone mineralization. Since vitamin D is a seco-steroid, its activity is indirectly expressed via VDR (The Vitamin D Receptor), VDR are found abundantly within the nucleus of the target cell, hence it's a Nuclear Receptor.[6] It is a known fact through various studies that VDR are ubiquitous in nature and hence are expressed in all the tissues of the body. Owing to its presence in extracellular sites it exhibits effects at different places in the body. The activity of vitamin D is exerted by its binding to the VDR, which then gets involved in variety of functions that includes regulation of calcium, vitamin D, Insulin like growth factor, signaling, inflammation and estrogen-related pathways. The multipronged involvement of vitamin D in potentially important and very intricate pathways, outline its importance in the etiopathogenesis of cancer.[7]

The Vitamin D Receptor

The vitamin D receptor VDR, belongs to NT transacting transcriptional superfamily of regulatory receptors. This superfamily of receptors includes steroid, thyroid hormone, retinoid-X receptors

and Retinoic acid receptors. VDR is encoded by a large gene of >100kb that is located on the chromosome 12q12. The gene encoding VDR consists of two promoter region, eight-protein coding exons and six untranslated exons. The promoter region is capable of generating multiple tissue specific transcripts. The responsive elements in the VDR are known to regulate a variety of cellular cycles and its processes, like the growth and differentiation of cells, apoptosis, invasion, metastasis of tumor cells that involves a variety of genes like the cyclin A, p21/WAF1, cyclin E, human c-fms, c-fos, c-myc, c-jun etc. Hence an assumption can be drawn that signaling pathways that are mediated by the VDR and genetic polymorphism of the VDR plays a prime role in cancer pathogenesis.[8]

Vitamin D action cascade

After entering the cell by crossing through the membrane proteins, vitamin D binds to the VDR, after binding to the vitamin D receptor, the VDR forms heterodimer with the Retinoid X Receptor RXR and then binds to the vitamin D responsive elements on the respective responsive gene.[9] Binding of vitamin D with the heterodimer and to their respective elements (VDREs) initiates transcription and translation which later leads to protein synthesis like the formation of osteocalcin, CBP (Calcium Binding Proteins) etc. the heterodimerization of VDR-RXR is an important key process that initiates the process of transcription which coupled with translation resulting in target protein synthesis, this complex results in the recruitment of c0-activators, histone acetyltransferases, the mediator complex subunit 1. The VDR-RXR complex translocate itself to the nucleus of the cell after binding to the VDREs which allows either the promotion or suppression of specific cellular events including Gastric cancers.[10]

Malignancies of the Esophagus and the role of VDR and Vitamin D

Cancer of the esophagus are some of the rarest forms of cancer that is primarily either squamous cell carcinoma or adenocarcinoma, the incidence of esophageal cancers and more so squamous cell carcinoma increase in patients with history of heavy alcohol consumption or smoking.[11] Dysphagia is the most common symptom that is presented in patients with this cancer and is difficult to diagnose in the initial stages. Dysphagia as a symptom is often seen in the advanced phase of the disease. In these patients the 5-year survival rate is roughly 15% and is frequently documented that most patients with this form of malignancy die within the first year after diagnosis. Quiet a few research studies have pointed out that VDR and Vitamin D allows for very early detection of esophageal malignancies and hence enables the clinician and the patient caregiver to opt for alternative therapeutic strategies. Apart from the mentioned there are no yet reliable markers for the diagnosis and detection of esophageal malignancies.[12] It is studied by quiet a few authors that the expression of VDR declines when the tumors reach the phase of de-differentiation and the translocation of VDR occurred in the phase of neoplastic transformation. Although there is no conclusive evidence on the role of Vitamin D in esophageal cancers but the expression of VDR is studied to be unregulated in cases of mucosa of Barrett's esophagus when compared to the normal squamous epithelium. Gastroesophageal reflux disease (GERD) forms the background for the development of esophageal cancer and in cases of Barrett esophagus the normal squamous stratified epithelium is being replaced by metaplastic columnar epithelium that predisposes to the development of malignancies.[13] This alteration occurs due to the alterations in gene expression and vitamin D is studied to regulate and modulate the mechanisms that contribute to carcinogenic changes in the mucosa of the esophagus.[14]

The cascade of events that occurs when reflux of gastric acid and bile comes into play due to the inflammation of the esophagus that result in the development of keratinocytes and release of pro-inflammatory markers that includes, Substance P, Platelet Activating factors and IL-8 (Interleukin-8), this recruits the blood leukocytes including Neutrophils and therefore stimulate the production of Nitric oxide, H_2O_2, Reactive Oxygen Species (ROS) and hypochlorous acid. These products of inflammation have the potential to initiate the genetic modification of the phenotypes and results in metaplasia that results in progression of mutagenesis and carcinoma progression in the esophagus. Calcitriol is hypothesized to alter the metaplastic and neoplastic changes in the esophagus by mitigating the effects of the COX-2 and inhibiting the genotoxic effects of the ROS, it also plays an important role in the direct metabolism of bile acids. It is interesting studied that calcitriol may play a direct role in the metabolism of bile acids. A toxic secondary bile acid called as Lithocholic acid plays an important role in carcinogenesis, this acid is catabolized by the cytochrome oxidase CYP3A4. Both Lithocholic acid and 1,25 (OH)2D is studied to interact with VDR and upregulate the process of transcription of CYP3A4, which is involved in the detoxification of bile acid thus reducing the risk of esophageal malignancies.[15]

Vitamin D3, VDR and Gastric Carcinoma

Carcinoma of the stomach is considered as the fourth most common malignancy worldwide and is often known to have very poor prognosis. This form of cancer can originate from any form of the stomach and is often missed in the early stages of the disease due to lack of evident symptomatology or due to reckless attitude of the patients in view of neglecting the symptoms that are often interpreted as gastritis. In vast crowd of people with cancer of the stomach. H. Pylori is implicated which is also called as Helicobacter Pylori. Apart form infection with H. Pylori, dietary factors in conjunction with chronic smoking and alcohol consumption also plays an important role. It is challenging to note that gastric cancer specifically the adenocarcinoma of the stomach is the most common form of malignancy that arises from the epithelium of the stomach. Other symptoms that are often nonspecific includes discomfort in the abdomen, indigestion, loss of appetite, belching etc. in the later phases of the disease chronic bleeding and acute bouts often lead to development of anemia.[16]

Various studies have highlighted the important role that is played by vitamin D in the tumorigenesis. High levels of vitamin D has been studied to reduce the risk of gastric cancers. An analog of calcitriol known as Paricalcitol is known to suppress the growth of cancerous/malignant cells by regulating the cell cycle, induces apoptosis of the malignant cells, reduces inflammation without inducing the generation of hypercalcemia. A well known studied by Bao et al., has found that calcitriol is directly linked with the induction of apoptosis of the gastric cancer cells and increases the expression of VDR and CYP24A1 which further supports the anti-malignant activity of the calcitriol in this condition.[17] It is also known that hedgehog signaling genes that includes patchhed1 and the Gli1 plays an important role in the progression and differentiation of the gastric cancer cells. Vitamin D acts through hedgehog pathways and signal inhibition thus cutting off the mutagenesis and carcinogenesis of the gastric cancer cells. VDR functional elements have been identified in the promoter sequences of phosphatases and tensin homolog (PTEN) which suggests the important role that is played by vitamin D in the regulation of PTEN expression and inhibition of carcinogenesis.[18] It also promotes apoptosis of the undifferentiated malignant cells of the gastric mucosa in specific the HCG-27, Vitamin D is also studied to modulate the extracellular macro-environment which prevents the gastric cells from turning into their malignant forms. Active forms of vitamin D has also been hypothesized to inhibit wnt gene and the cross talks and signaling pathways between the tumor cells and its microenvironment. Hence it can be seen that Vitamin D is an important and significant prognostic factor in patients with gastric malignant conditions. And deficiency of Vitamin D may be associated with an increased incidence of gastric carcinoma and poor prognosis.[18]

Hepatocellular cancer and Vitamin D

Hepatocellular cancers are a group of tumors that often metastatic in nature and derived from other organs of the body which includes breast, lungs, colon and kidneys. Primarily two types of carcinomas originate in the liver, cholangiocarcinoma (CCH) from cholangiocytes lining the bile duct and hepatocellular carcinoma (HCC) from the hepatocytes or liver cell. Cirrhosis or viral hepatitis predisposes to the development of HCC, whereas cholangiocarcinoma is the result of damage to the bile duct from disease primarily involving cells lining the bile duct like primary sclerosing cholangitis. It is well known fact that both HCC and CCH express high levels of CYP24A1, which leads to reduced levels of Vitamin D, thereby allowing tumorigenesis, it was seen in these studies that treating the patients with Vitamin D resulted in decreased proliferative rates in cells lines of CCH and HCC both.[19]
It is well established that Transforming Growth Factor beta (TGF- β) and its signaling cascades is aberrant in many hepatocellular and gastrointestinal malignancies with sophisticated multimodal role that promotes epithelial-mesenchymal transition for suppressing and promoting carcinogenesis, this factor is considered as the driving force for these specific malignancies and mediates its action through type I and Type II serine-threonine receptor kinases. When the TGF-β gets activated through binding of the ligand, it activates Smad, specifically

the Smad2 and Smad3 that forms complex with Smad4 and subsequently gets translocated into the nucleus. The Smad complexes that get activated recruit's co-activators and co-repressors that results in regulation of a multitude of target genes and transcription processes. Target genes that get activated results in complex outcomes which includes connective tissue deposition, arrest of the cell cycle in the G1/S phase, induction of apoptosis, immune suppression as well as tumorigenesis. It is also studied that Vitamin D acts as an antifibrotic factor or an agent that limits fibrogenesis in both bone marrow mesenchymal stem cells and cells of the liver/hepatocyte. Vitamin D causes increased expression of VDR, the proliferation of hepatocytes specifically the cells belonging to the stellate category are inhibited, it also inhibits expression of cyclin D1, tissue inhibitor of metalloproteinases and collagen. The active metabolites of Vitamin D cause increased expression of metalloproteinases 8 which degrades collagen and lowers the production of collagen 1 and collagen III and hence inhibiting fibrosis or limiting its activities. It is also studied that Vitamin D analogs are also potent cytostatic and apoptotic agents in hepatocellular malignancies which expresses VDR, it also suppresses β-catenin which is implicated in the hepatocellular carcinoma and cirrhosis.[20]

Relationship between Vitamin D and Pancreatic cancer

In its most aggressive form pancreatic cancers are considered as life threatening disease with highest mortality rates among all major types of carcinomas, it is a malignant condition that has the highest comparative mortality amongst all major types of cancers prevalent in the world. It arises from cells that are usually transformed from the normal cells of the pancreas. In the exocrine part of the pancreas Adenocarcinoma arises and is the most aggressive and deadly form of cancer with poorest prognosis. One of the confirmed risk factors that causes pancreatic cancer is smoking. Lot of studies have been carried out to know the association, intent of vitamin D therapy and progression of pancreatic cancers. Scientifically it is well determined that in both normal and Aden carcinomatous pancreatic condition the enzyme which catalyzes the double hydroxylation process of Vitamin D synthesis is expressed from the ductal cells. It is also studied that the VDR is decreased in its expression in numerous pancreatic tumor cell lines when compared to normal pancreatic cells. A study conducted by Jones et al., based on the genetic analysis have determined that a core set of 12 pathways and signals are involved in pancreatic cancer development, Calcitriol analogs can have anti-tumor effects. Analogs of calcitriol inhibits tumor cell proliferation and their growth and are known to arrest the cell at the G1/S phase of the cell cycle, they also induce apoptosis, inhibits, or suppress the mitigation and invasion of the pancreatic cancer cells in various cell lines and human pancreatic cancerous tissues as well as xenografts of pancreas. These analogs are studied to effect the Akt pathway that results in upregulation of cyclin-dependent kinase inhibitors p21 and p27 and downregulation of cyclin D3, CDK 4 and 5. Various other potential pathways are known to operate which are inhibited by vitamin D in its active form that results in inactivation of the Smad, downstream hedgehog, cadherin switch block, F-actin synthesis repression and decrease in the synthesis of metalloproteinases 2 and 9. The analog of calcitriol 19-nor-2α-(3-hydroxypropyl)-1α,25(OH)2D3 has shown to inhibit epithelial to mesenchymal transition through downregulation of Snail, Slug, and Vimentin expressions. It is known fact that VDR acts as master genomic regulator of the pancreatic cell that activates cellular programming from pancreatic carcinogenic stroma. Pancreatic cancers express the VDR, and its expression is altered in pancreatic cancers, calcitriol analogs may affect the pancreatic cancer tissue by mechanisms that do not involve direct interaction with its receptors.[20]

Association between Vitamin D and Colorectal cancers

Colorectal cancers (CRC) are malignancies anywhere in the colon, rectum, or appendix. Most of the carcinomas pertaining to colon and rectum are linked with lifestyle of a person and increasing age, genetic abnormalities play a minor role in the genesis of colorectal cancers. By it's innate nature CRCs grow from the mucosal cell lines of the gut which then grows if untreated into the muscular layers of the bowel. This type of carcinogenesis is well triggered by the environmental chemicals, agents, radiations and infectious disease-causing pathogens and also has a genetic basis for its progression which includes (cellular mutation, regulation of the cells of the immune system and ultimately hormone dysfunction. CRC comprises of group of symptomatology which range from worsening constipation, bloody stool/melena, loss of appetite and weight loss.[21] These symptoms aggravate with advancing age. Vitamin D via its Vitamin D Receptor VDR regulates proliferation, de-differentiation, apoptosis and many more in a fashion that is autocrine within the colonic epithelium, VDR over expression is associated often with P13k-AKT pathway and its KRAS mutations, like any other cancer of the gastrointestinal tract, treatment with Vitamin D, the treatment with Vitamin D for Colorectal Cancers CRC has to be closely monitored and personalized.[22] It is a plausible associated that polymorphism of VDR gene may be the possible risk factor the genesis of colorectal cancers. It is also studied that Vitamin D as a hormone is associated with the severity of intestinal injury, deficiency of vitamin D is often found in patients with Irritable Bowel Disease (IBD) and cancer of the colon (CRC), It is proposed that treatment with calcitriol can shift the gut microflora and protect the patients suffering from the debilitating condition like IBD and other forms of cancers.[23]

CONCLUSION

Vitamin D in its active form is bestowed with multipronged pleotropic effects with a prominent effect in carcinogenesis more so in gastrointestinal malignancies. It confers beneficial effects in patients suffering from various types of cancers and gastrointestinal malignancies. Its action is regulated via the Vitamin D Receptors VDR through which it influences various cellular events that includes carcinogenetic cascades including inhibition of cellular differentiation, proliferation, metastasis, invasion of tumor, tumor-angiogenesis, cycle arrest of the cancer cells in the G1/S phase and apoptosis, hence these implicate the intricate connection between the beneficial role of vitamin D and Gastrointestinal Malignancies. To establish concrete evidence, it is important to carry of large multicentric, randomized therapeutic interventional trials using different dosing regimens of vitamin D along with other anti-cancer therapeutic interventions to establish the fact on the beneficial effects of Vitamin D in its active form to influence the occurrence, severity, prognosis and mortality associated with Gastrointestinal cancers.

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