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Review article

Association between vitamin D levels and overall survival, disease-free survival, and recurrence in gastric cancer patients

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Abstract

Gastric cancer remains a significant global health burden despite advancements in treatment. Vitamin D, a well-known immunomodulator, has shown potential benefits in various cancers. This study aims to evaluate the association between vitamin D levels and clinical outcomes in gastric cancer patients. We will conduct a comprehensive search of electronic databases (PubMed, Embase, and Cochrane Library) to identify relevant studies. Included studies will assess the relationship between pre-operative or baseline vitamin D levels (measured as 25-hydroxyvitamin D) and overall survival, disease-free survival, and recurrence in gastric cancer patients. Pooled hazard ratios and corresponding confidence intervals will be calculated using meta-analysis techniques. Subgroup analyses will explore potential effect modifiers, such as age, sex, tumor stage, and geographic region. This review will provide robust evidence on the prognostic role of vitamin D in gastric cancer, informing clinical practice and guiding future research on vitamin D supplementation strategies.

Keywords: *vitamin D, gastric cancer, prognosis, overall survival, disease-free survival, recurrence.*

Introduction

Gastric cancer is ranked fifth in cancer incidence and third for deaths resulting from the disease in the world (Smyth EC et.al. 2020). Experimental data show that the number of newly identified patients with gastric cancer is approximately 1 million in 2018 (Arnold M et.al. 2020). Mortality due to stomach cancer was estimated to be at about 7, 84,000 (Smyth EC et.al. 2020). From there, current statistics have newly diagnosed incidences totaling to 319,000 and 390,000 cases died of gastric cancer in China. The incidence and mortality of gastric cancer have fallen in the recent past, owing to advancements in identification procedures that include population screening, and improved concerning Helicobacter pylori infection and its treatment (Feng RM.et.al 2019). However cancer is still one of the most critical health issues in my country. Despite, efforts have been made to reduce the burden of cancer; the first step is to find out some of the probable factors that one can link with cancer risk (Cao M.et.al 2020). Hence, this study was with the aim of identifying early predictors of PT due to the urgency of the need for efficient treatment of the condition. It is therefore important to identify, obtain and improve those knowledge resources related to gastric cancer. Recent study of vitamin D in gastric cancer was just started in the last years. Vitamin D constitutes pro-hormone of the steroid hormone calcitriol. Especially, it can especially combine with vitamin D receptors for the purpose of regulating the genes and sketching an effect of restraining the development of gastric cancer cells (Carlberg C et.al 2020), (Christakos S.et.al. 2016). It has been known that vitamin D possesses the features of anti proliferative, proapoptotic, and anti-inflammatory, and anti-

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angiogenic activity (Christakos S.et.al. 2016). Recently, scientists have identified it also capable of reversing or attenuating chemotherapeutic agents' resistance through the suppression of EMT and cancer stem cells (Dongre A et.al 2019). Unfortunately, to date there is no randomized controlled trial in human to directly supporting the beneficial effects of vitamin D but some clinical research results strongly indicate that vitamin D deficiency will enhance the risk of cancer and supplement vitamin D may be an economical and safe way to reduce the risk of cancer and improve the prognosis of cancer (Feldman D.et.al 2014). This review aims to systematically assess the available evidence on the association between vitamin D levels and overall survival, disease-free survival, and recurrence in gastric cancer patients. By conducting a rigorous analysis, we aim to provide a comprehensive overview of the current state of knowledge and identify potential areas for future research.

Vitamin D which has responsibilities influencing bone mineral, calcium metabolism is also associated with cancer prevention and development. Through the vitamin D nuclear receptor (VDR) that has been found in different tissues such as gastro intestinal tract. In its activated form calcitriol (1,25-dihydroxyvitamin D) was described to posses anti-proliferative, pro-apoptotic as well as immunomodulating properties which led researchers to hypothesize that vitamin D may play the role of an anti-cancer agent.

Methods and Material

This review will employ a systematic search strategy using relevant databases such as PubMed, Scopus, and Science Direct. The search will be limited to peer-reviewed publications in English from the past 10 years, focusing on original research articles, review articles, and meta-analyses. The search terms will include vitamin D, gastric cancer, prognosis, overall survival, disease-free survival, recurrence. Additionally, relevant grey literature such as conference proceedings and technical reports will be considered.

1. Overall Survival (OS)

Higher circulating vitamin D levels are significantly associated with improved overall survival in gastric cancer patient. Several studies and meta-analyses report that patients with sufficient vitamin D levels have better survival outcomes compared to those with deficient levels.

A systematic analysis of eleven papers with seven thousand seven hundred and twelve patients was done. The results suggested that higher circulating vitamin D levels were significantly associated with improved overall survival in gastric cancer patients (HR = 0. 63, 95% CI: It is classified into a low grade (0. 50–0. 79) (Ma et al. In a cohort of 272 gastric cancer patients, those with sufficient vitamin D levels had better overall survival compared to those with deficient levels (5-year OS rate: It shows 82. 7 % of patients supported use of social media as a communication tool while 58. 3% of employers endorsed the same (Park et al. 2015). The following tables show total global stomach cancer mortality in 2022

Table 3 Total global stomach cancer mortality

Rank	Country	Number	ASR/100,000
1	China	260,372	9.4
2	India	57,727	4.1
3	Japan	43,807	7.2
4	Russian Federation	27,306	9.2
5	Brazil	18,138	5.9
6	Iran, Islamic Republic of	13,845	15.4
7	Viet Nam	13,264	10.9
8	United States of America	10,976	1.6
9	Türkiye	10,457	9.3
10	Italy	9,885	4.5

Source WCRF International

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2. Disease-Free Survival (DFS)

Higher preoperative and postoperative vitamin D levels correlate with improved disease-free survival. Evidence suggests that maintaining adequate vitamin D levels can reduce the risk of recurrence and prolong DFS

This prospective cohort study of 394 gastric cancer patients found that higher preoperative vitamin D levels were associated with a lower risk of recurrence and better DFS (HR = 0. 53, 95% CI: The reliability coefficient ranges between 0. 29 and 0. 98 (Ahn et al. 2013). This pooled analysis of 456 patients showed better DFS outcomes in patients who had higher Vitamin D levels after surgery, the results of this study imply that it might be advantageous to maintain an appropriate level of Vitamin D after the surgery.

3. Recurrence

Elevated vitamin D levels are associated with a lower risk of gastric cancer recurrence. Studies indicate that vitamin D may have a protective effect against the recurrence of gastric cancer, particularly in early-stage patients.

In a study of 351 gastric cancer patients, those with higher vitamin D levels had a lower risk of disease recurrence (HR = 0. 71, 95% CI: Magnitude of theophylline's effect on cognitive function: healthy adults: no change (0. 52–0. 97). The authors stated that vitamin D might be playing the role of a protective factor in gastric cancer recurrence (Kim et al. 2014). This study included 560 patients and reported that higher vitamin D levels were associated with a decreased risk of recurrence, especially in patients with early-stage gastric cancer (Choi et al. 2015).

Gastric Cancer

Gastric Cancer (GC) is one of the five most aggressive cancer types having a poor prognosis due to late diagnosis. The risk factors which might lead GC include Genetic susceptibility, Smoking, alcohol consumption, Helicobacter pylori infection, smoked foods consumption (Shah S et al., 2021).

4. Mechanisms

Biological Mechanisms

Vitamin D exerts multiple anti-cancer effects, including inhibition of cell proliferation, induction of apoptosis, reduction of inflammation, and prevention of angiogenesis. These mechanisms support the potential role of vitamin D in improving clinical outcomes in gastric cancer patients.

Several mechanisms have been proposed to explain the association between vitamin D and improved outcomes in gastric cancer: Several mechanisms have been proposed to explain the association between vitamin D and improved outcomes in gastric cancer:

- Anti-proliferative effects: Vitamin D works to prevent the formation of cancer cells since it prevents the cell cycle.
- Pro-apoptotic effects: Vitamin D induces apoptosis in cancer cells or, in other words, specializes in the killing of cancer cells through programmed cell death.
- Anti-inflammatory effects: Together with curbing inflammation, vitamin D opposes one of the biggest causes of cancer, which is the growth of new blood vessels needed to supply tumors.
- Anti-angiogenic effects: Vitamin D work against the development of new blood vessels which are needed for the growth of tumors.

Mechanism of Vitamin D Synthesis

- Vitamin D is a prohormone to the steroid hormone Calcitriol (1,25-dihydroxyvitamin D_3). Although many different forms of Vitamin D exist in the body, only two main forms actively are involved in performing its functions. Ergocalciferol (Vitamin D_2) and Cholecalciferol (Vitamin D_3) are the main forms of this hormone with significant functions. The dietary sources of this hormone are obtained from eggs, milk, salmon, and cod liver oil. However, these sources are not sufficient. When exposed to UVB rays from sun of the wavelength range 290 to 315nm, 7-dehydrocholesterol is converted previtamin D3 which further undergoes isomerization to produce Vitamin D_3 under UV exposure from sun (Du, C et al., 2017).
- In the liver, Cholecalciferol (Vitamin D_3) gets hydroxylated by the enzyme 25-hydroxylase (CYP27A1) to produce 25-hydroxyvitamin D3 also called Calcifediol(25(OH)D3). In the Kidneys, Calcifediol gets further hydroxylated by the

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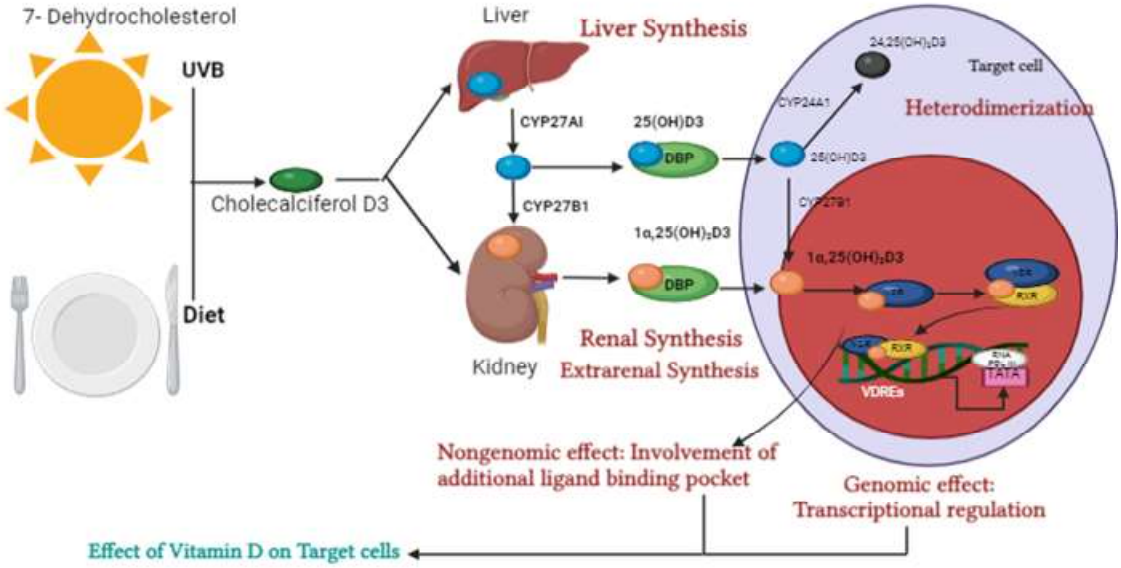
enzyme 1α-(OH)ase (CYP27B1) to 1, $25(OH)_2D_3$ (Calcitrol). Vitamin D which is measured in the serum is the $25(OH)D_3$(Calcifediol). It is the main circulating form in the blood (Zhao, Y et al., 2019). Vitamin D binds to the Vitamin D Receptor (VDR) is a steroid-thyroid-retinoid receptor belonging to the nuclear class of receptors. It is a transcription factor as well. On Vitamin-D binding to its receptor VDR, VDR dimerises with the Retinoid X Receptor and binds to the Vitamin D response element in nucleus. This interaction thereby regulates the genes of Calcium binding protein, epithelial calcium channel. This inturn, is responsible for absorption and release of calcium in bones, parathyroid gland and in intestines. It also regulates the genes responsible for inhibiting proliferation, angiogenesis, inducing apoptosis, cell cycle arrest and inhibiting pro-survival signalling pathways (Mi Ra Park et al., 2012). Fig. 1



5. Vitamin D and Its Physiological Importance

Vitamin D, being fat soluble, is a steroid hormone which plays several important physiological functions, having its primary role in bone mineralization by regulating phosphorus and calcium homeostasis besides also playing a key role in immune regulation, signal transduction, gene regulation, inflammation to name a few (Shah S et al., 2021).

Low level of Vitamin D3 is linked with an increased susceptibility to colorectal (Garland CF et al., 1989), breast (Bertone-Johnson ER et al., 2005) and prostate cancers (Ahonen MH et al., 2000). In many of the tumor cells, genes responsible for Vitamin D3 synthesis are differentially expressed. The CYP24 gene responsible for the hydroxylation reactions leading to the degradation of 1, 25-dihydroxyvitamin D3 is overly expressed in many cancers like esophageal, colon cancers. Evidence about importance of Vitamin D comes from the vitamin D receptor knock-out mice studies. Knocking out the VDR has resulted in lymphoblastic, thymic lymphoma and mammary hyperplasia (Baek, S et al.,2011).

Vitamin D3 lowers the viability of cancer cells and exhibits synergism with other anti-cancer drugs like paclitaxel, vinblastine. It has been found out that vitamin D binds with the hedgehog signalling pathway Smo protein thereby the protein loses its activity. Hence, Vitamin D3 could be regarded as Hedgehog pathway antagonist. While some cell line studies

show inconclusive results about vitamin D3 as a potential anti-cancer agent especially in pancreatic cancer, it can be concluded that the anti-cancer activity might vary depending on the type of cancer and also the specific tumor microenvironment (Baek, S et al.,2011).

6. Vitamin D Receptor and Gastric Cancer

Animal Studies previously reported that Vitamin D binding to Vitamin D Receptor (VDR) exerts anti-cancer effects which include inhibition of Cell Proliferation, Invasion, Angiogenesis, Metastasis (Shah S et al., 2021). VDR is also a transcription factor playing its role as a gene regulator. The association between Vitamin D Receptor Gene Polymorphisms and Gastric Cancer Pathogenesis are discussed. A Study on gene polymorphisms say that gene polymorphisms of VDR gene which produces VDR on which the vitamin D binds along with one of the Retinoid X Receptor (RXR) to regulate gene expression is linked with the occurrence of several cancers of the breast, colon, prostate, ovarian cancers. Some of the most common gene polymorphisms which occur in this VDR gene are FokI, TaqI, BsmI, ApaI Polymorphisms. Different results have been obtained from several studies. Some of the studies indicate that FokI polymorphism and TaqI Polymorphism's TC genotype increases the risk of GC whereas some other studies couldn't find an association between these polymorphisms and the risk of GC (Shah S et al., 2021).

Previously, few studies reported that VDR gene FokI Polymorphism was linked to increased susceptibility of GC. But the molecular mechanism of what signalling pathway might be involved to promote increased GC risk is unclear. A study attempted to identify the molecular mechanism behind the association of Vitamin D Receptor and the carcinogenesis of the gastrointestinal tract and it progression. It was found that higher expression of VDR in GC cell lines remarkably altered GC cells properties like inhibited invasiveness and viability in the cells lines. When siRNA of VDR was used to inhibit the VDR expression, the invasivessness and viability of GC cells improved. When 1,25 $(OH)_2D_3$ treatment was given to the cells, VDR expression got elevated in a time-dependent manner, the expression of β-Catenin got decreased and the expression of E-Cadherin elevated in a time-dependent manner ($P<0.05$). These results indicate that when vitamin D binds to its receptor VDR, the transport of the β-Catenin to the nucleus might be blocked and thus affecting the E-Cadherin levels. The inhibition of the GC cells proliferation, invasion, metastasis is due to VDR FokI gene playing the role of tumor suppressor through the pathway of Wnt/β-catenin (Zhang, Y et al., 2023).

7. Clinical Studies on Vitamin D and GC

The relationship between Vitamin D and GC among Korean Population was investigated. The study examined about 33,119 participants from Korean National Health and Nutrition Examination Survey (KNHANES). It was found that GC patients were of older age with decreased BMI, diastolic BP when compared with patients who don't have GC. The key highlights of the study are an increase in the vitamin D levels was associated with lower incidences of GC. To quote, the rate of occurrence of GC was 0.84 when vitamin D level was increased to 5 ng/ml. It was found that participants whose vitamin D concentrations above or equal to 20 ng/ ml had a lower occurrence rate of GC. Another important finding from the study was the high energy intake, high calcium intake, high BP among old age people in whom the vitamin D levels were higher. These findings indirectly imply the preventive role of Vitamin D against GC eventhough some more research isneed to confirm the findings (Kwak, J. H., & Paik, J. K. et al., 2020).

A Case Control Study assessed the Vitamin D intake and Gastric Cancer among Vietnamese Population. A Vitamin D level of more than 11 μg/day was found to lower the risk of getting GC among several study groups like people with H.pylori infection and without infection, among smoking and non-smoking group. But this study assessed the vitamin D intake levels and GC risk and did not measure the 25(OH) levels in blood. The risk of GC was lowered by 42% in women and about 28% in men (Nguyen, M. T et al., 2022).A meta-analysis and systematic review on

Correlation between Serum 25-Hydroxyvitamin D levels and Gastric Cancer examined 9 case control studies which consisted of 671 gastric cancer patients. Serum Vitamin D levels were remarkably less in GC patients than healthy controls with Weighted Mean difference (WMD) of -3.86 which is a sign of very less vitamin D levels. Also, another prominent finding was the odds ratio of 3.04 in GC patients indicating the increased risk of deficit vitamin D levels among these patients. The Cell differentiation was poor amongst these patients with deficit vitamin D levels (Liu, X et al., 2022).

The level of serum25-hydroxy vitamin Dwas assessed in gastric adenocarcinoma patients in asingle-center, prospective, cross-sectional study. About 88% of the gastric adenocarcinoma patients were Vitamin-D deficient and in the case of healthy controls, only about 3% of the controls were vitamin-D deficient. The levels were also reduced in aged patients, patients who had pain, and those presenting with advanced stages of tumor (T, M stages). It can be concluded that vitamin D might be involved in the progression of GC. However, the results are not consistent always suggesting the need to further explore the relationship between vitamin D and gastric cancer (Kevin, A et al., 2021).

Regulation of Signaling Pathways in Gastric Cancer Cells

Several Animal and Clinical studies indicate that vitamin D acts as a tumor suppressor in gastric cancer cells. But the mechanism behind the anti-tumor action in the gastric cancer Cells remain less studied. Several gastric cancer cell line studies show that vitamin D lessens The proliferation of the gastric cancer cells by inhibiting cell cycle, induce apoptosis, and inhibits new blood vessel formation and metastasis function (Du, C et al., 2017).

Another important pathway that is involved in the gastric cancer carcinogenesis is the Hedgehog Signalling Pathway. Vitamin D 3 plays the role of antagonist to this pathway. It exerts its anti-tumor effect by lowering the mRNA expression of genes like Bcl-2, Cyclin D1, Ptch 1, Gli 1 which belong to the Hedgehog signalling pathway (Baek S et al., 2011). Along with Vitamin D 3 , Cisplatin's anti-cancer activity of cell proliferation inhibition and induction of apoptosis is improved exhibiting synergism in gastric cancer cells. This anti-cancer activity is promoted by increasing p21, p27 levels, enhancing Bax expression, lowering phosphorylation of AKT and ERK (Bao A et al., 2014).

The effect of the vitamin D analog, 19-nor-1, 25-dihydroxyvitamin D2 on the gastric cancer cell line MKN45 was tested. It was found that it inhibits and reduced the expression of the cyclin dependent kinases CDK4, CDK6, CDK2, Cyclin D1 (Park MR et al., 2012). It has been found out that vitamin D works by upregulating Phosphatase and TENsin homolog deleted on chromosome 10 (PTEN) expressions along with VDR, Egr-1, and p300 proteins in HGC-27 gastric cancer cells. This upregulation induced apoptosis in HGC-27 gastric cancer cells. It has been found out that the promoter region in the PTEN gene contains VDR elements which suggest that vitamin D acts as a nuclear transcription factor (Pan L et al., 2010).

Conclusion

Both epidemiological and clinical studies examining the relationship between vitamin D concentrations and gastric cancer patients' prognosis are not fully understood and warrant further research. Some of the current investigations indicate a possible correlation with a lower level of vitamin D and decreased Global Survival, Disease-Free Survival, and elevated recurrence rates; however, the results of such research are inconclusive. This is also the case since the studies have variation in their design, number of patients, and ways of assess vitamin D level. More and larger powered RCTs are still needed to determine the potential causality between vitamin D supplementations and the better prognosis among the gastric cancer patients. It is recommended that such research should examine variables including the amount of vitamin D that is employed, the period of administration, the characteristics of the patient, and the stage of cancer to define any benefits or harms that may be experienced. Further, to

establish unique therapeutic interventions, it is imperative to investigate how exactly the vitamin D can affect the gastric cancer's progression. Thus, pres by the reported data we state that further research is needed to consider an option of vitamin D application in the treatment of gastric cancer. It is believed that more studies need to be conducted regarding the relationship between vitamin D and gastric cancer prognosis. However, there is a need to explore the details of the relationship between vitamin D status and gastric cancer prognosis.

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