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RESEARCH ARTICLE

THERAPEUTIC EFFECTS OF VITAMIN D IN PATIENTS WITH ACTIVE INFLAMMATORY BOWEL DISORDER: EXAMINING THE RELATION BETWEEN VITAMIN D INTAKE AND DISEASE ACTIVITY

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Abstract

Background: Inflammatory bowel diseases include Crohn's and ulcerative colitis . They have become more common diseases and lifelong problems for individuals, despite the availability of many medication and surgical alternatives. To achieve the optimum benefits, vitamin D is used to lower disease activity.
Objective: This study helps us show the impact and therapeutic effect of vitamin D in active Inflammatory bowel disorder .
Methodology: PubMed, the Cochrane Library, and ScienceDirect are the databases searched for randomized controlled trials (RCTs) and reviews. After quality appraisal and cross checking the literature, this systematic review is carried out grounded on Preferred Reporting Items for Systematic Review and Meta-Analysis 2020 (PRISMA 2020) guidelines. A total of 11 studies which include nearly 1500 subjects showed that there's an positive association between VIT D and disease severity .
Results: The results suggests that vitamin D administration can significantly lower the inflammation in the gut. An inexpensive VIT D reduced inflammation and drastically bettered the patient lives.
Conclusion: To completely understand the complex Relationship between Vitamin D and Inflammatory Bowel Disorder, Large population-sizes trials are highly demanded for further identification and understanding the efficacy of vitamin D with conventional therapy.

Introduction:-

IBD is a chronic disease that mostly includes ulcerative colitis (UC) and Crohn's disease (CD). While the pathophysiology of IBD is unknown, it is widely accepted that the environment, genetics, and viral factors all

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contribute to the development of the disease, and both UC and CD have a significant and overlapping genetic component. IBD occurrence is currently increasing worldwide, however the causes for this remain unclear. - [1].

In the human body, vitamin D participates in the metabolism of calcium, phosphorus and other substances, and it is believed to be highly associated with cancer as well as other chronic diseases Auto immune disorders- [2]. There appears to be an important role for vitamin D deficiency in the development of a wide range of inflammatory diseases- [3,4]

Lack of vitamin D in IBD patients is most likely owing to poor absorption caused by the disease, but it has also been hypothesized that the shortage may lead to the development of IBD and effect disease severity. This is corroborated by research in diverse populations that reveal the relationship between vitamin D level and the development of IBD and its activity – [5,6].The level of vitamin D is probably not related to disease type as patients with UC and CD both have similarly low levels. Local expression of vitamin D probably integrates innate as well as adaptive immunity in the intestinal epithelium to promote barrier integrity and redirect from the inflammatory response.–[7]. Nevertheless, becausevitamin D deficiency is also strongly related to race and genetic background, it is important to understand how vitamin D levels are associated with IBD.This study helps us show the impact and therapeutic effect of vitamin D in active Inflammatory bowel disorder.

Methodology:-

This meta-analysis was carried out in the accordance with the preferred items for systematic review and prism guidelines- [35]

The literature was searched in the PubMed, googlescholardatabase. The regular keywords used in the search for vitamin D are as follows: Vitamin D, Cholecalciferol, Calcitriol, Drisdol, 1,25dihydroxycholecalciferol, Ergocalciferol, VitaminD2, VitaminD3; For Inflammatory bowel disease are as follows -IBD,Ulcerative Colitis, Crohn'sDisease. The Boolean search strategy was applied using "OR" in the regular keywords, giving 92,392 and 49,116 results for Vitamin D and Inflammatory bowel disease". Regular keywords were then combined using the Boolean term "AND" that generated 1,123. We also used Medical Subject Headings (MeSH) keywords such as "Vitamin D" and "inflammatory bowel disease" gave 101,075 and 118,265 results. The Boolean term "AND" was implemented on MeSH keywords, which gave us 554 results.

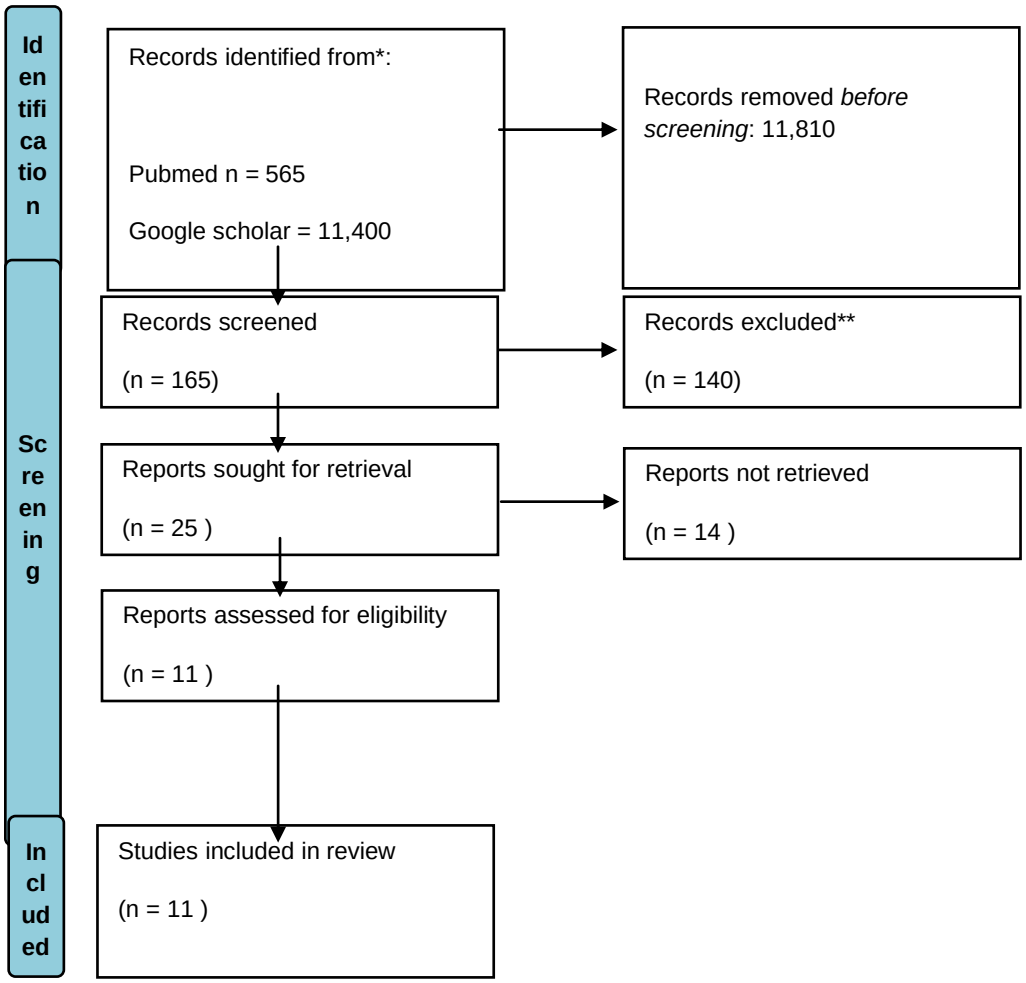
Inclusion criteria - Two investigators [vsr,pkv] screened each article title and abstract to determine eligibility independently first

Then the studies included by both reviewers were compared and disagreements were resolved by consensus. When the consensus couldn't reach between the two investigators, the third independent investigator who did not participate in original screening decided the eligibility.

The following inclusion criteria was used.
1-Free full text available
2- studies published in English language
3- observational studies and randomised control trail
4- systematic and narrative reviews
5-studies after 2017

Exclusion criteria -
1- The exclusion criteria include editorial, posters, exclusively animal studies
2- irrelevant studies

Only the studies meeting the above criteria were evaluated for eligibility in the final review.
After all the inclusions and exclusion, the number of papers were 165. These papers were screened for relevant topic and total number articles retrieved is twenty-five.



Quality Assessment Tools

Two investigators evaluated the risk of bias, using the Newcastle-Ottawa questionnaire for the observational studies (Table 1) and Cochrane risk-of-bias tool (Table 2) for clinical trials. We only included studies that had scores six and above in the Newcastle-Ottawa questionnaire for the observational studies and RCT, we only included studies that were judged as "low-risk" of bias in each of the domains. Disagreement was by consensus.

Author	Is the case definition adequate?	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls based on the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non resp rate
Zhao J et al. 17	1	1	1	1	1	1	1	0
Gubatan J 18	1	1	1	1	2	1	1	0
Lin X 19	1	1	1	1	1	1	1	0

Zhu C 20	1	1	1	1	1	1	1	0
Gao H 21	1	1	1	1	1	1	1	0
Jinzhong Li et al 22	1	1	1	1	1	1	1	0

RCT	Random sequence generation	Allocation concealment	Selective reporting	Binding participants	Blinding outcome assessment	Attrition bias	Other bias
Bincy P Abrahm - [23]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Bendix M- [24]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Karimi S -[25]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Sharifi A-[26]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Mayur Garg 27	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Results and Discussion:-

Inflammatory bowel disease

Inflammatory bowel disease (IBD) is a chronic condition that causes gastrointestinal tract inflammation. Crohn's disease can affect the gastrointestinal barrier from the mouth to the perianal area, whereas ulcerative colitis primarily affects the colon and rectum. Currently, pathology is caused by different aetiologies involving immunological elements, dietary patterns, smoking, drugs, and others. – [28 , 29]

Crohn's disease and ulcerative colitis are typically characterized by diarrhoea with or without mucus and abdominal pain. The intensity of symptoms increases in flare-ups and may include fistulas, abscesses, and strictures in Crohn's disease and bleeding, perforation, pseudo polyps, and toxic megacolon in ulcerative colitis -[30].In addition to the gastrointestinal damage, some patients may develop extraintestinal symptoms whose persistence is associated with exacerbations of illness–[31]

Management of IBD includes multidisciplinary approachinvolving from immunomodulatory agents to surgicalresection –[32].Furthermore, 50% of Crohn's disease patients and 20% to 30% of ulcerative colitis patients typically require surgery during active periods. In both UC and CD, the standard course is recurrent flares and remissions, but stable patients more often stay stable (a patient with clinically inactive disease has an 80%-90% probability of remaining so in the following year), and those with flares more frequently relapse (a patient with clinically active disease has a 70%-80% chance of relapse the following year) –[33].Vitamin D is an essential fat-soluble vitamin. Its primary role is to regulate calcium and phosphorus balance, which promotes bone mineralization. Vitamin D can be obtained from a variety of foods, supplements, and from the skin when exposed to sunlight. It comes in two forms: vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). However, because both forms are inert, they must be hydroxylated twice to activate the final product. The liver and kidneys activate enzymes 25-hydroxylase and 1alpha-hydroxylase to create 1,25-dihydroxyvitamin D3 (1,25(OH)2Vitamin D3), which has physiological benefits. – [34].

Role of VIT D In IBD

UC and CD are marked by a chronic and relapsing that are immunologically mediated. IBD develops through a variety of ways. One is mostly induced by T cell induction. It has a significant impact on Intestinal microbiome by protecting from intestinal bacteria. The process could have an impact on the gut epithelium. Dysregulated immune responses have apparently displayed to play a clear role in the development of UC and CD-[8].Cytokines such as TNF alpha, IL-2, IL-6, and IFN-α contribute to chronic intestinal inflammation in IBD. Vitamin D is a key regulator of the innate immune response to infection. Its insufficiency has been linked to reduced immunity. Vitamin D3 promotes the preferred development of T cells into T regulatory cells.–[9]. As a result, the optimum level of vitamin D serves as the first line of defence against pathogenic organisms while also preventing uncontrolled immune system activation, which can be harmful. A large prospective study has found that people with extremely insufficient amounts of vitamin D were at risk of developing Crohn's disease – [10]

Vitamin D promotes the expression of antimicrobial peptides like cathelicidin and defensin β2 in various lines of human cells, notably myeloid cells, monocytes/macrophages, and neutrophils. [28-31].A study found that treating human colon cells with 1,25(OH)2D increased cathelicidin and IL-10 levels, decreased TNF-α, and reduced Escherichia coli growth. 11. VIT-D has numerous effects on both the innate and adaptive immune systems by activating anti-inflammatory pathways– [12].

Various Mechanisms through which VIT D Exerts itsAnti-inflammatory effects-

(i) Notably, calcitriol suppresses the creation of pro-inflammatory cytokines by monocytes and macrophages. (ii) lowers macrophage surface expression of major histocompatibility complex (MHC)-class II molecules, lowering macrophage antigen presentation and T-cell stimulatory capacity [13]. (iii) promotes the transition of macrophage polarization from a pro-inflammatory phenotype (M1, or "classically activated" macrophages) to an anti-inflammatory phenotype (M2, or "alternatively activated" macrophages) - [14]. (iv) controls dendritic cell development and function, lowering antigen presentation capacity and increasing tolerogenic capacity -[15]. (v) promotes the transition of T cells from a "effector" to a "regulatory" and anti-inflammatory phenotype by enhancing Th2 cells while lowering Th1 and Th17 cell development [35]. vi) Upregulates Tregs -[16] .

AUTHOR OF STUDY	YEAR OF PUBLICATION	NO OF SUBJECTS INVOLVED	FOCUSED SUB-TOPC	STUDY RESULTS
BINCY et al- [23]	2023	88	Role of VIT D In endoscopic improvement of IBD and serum CRP levels.	Study showed patients on vedolizumab for both UC and CD higher pre-treatment vitamin d levels were associated with higher endoscopic improvement of disease severity and marked reduction of CRP levels.
Bendix et al – [24]	2020	40	The expression of PD-1, PDL-1and surface activation markers were analysed who received 1200IU vitamin D3 vs placebo	PD-1 expression upon T cell stimulation was increased in CD4+CD25+int T cells in vitamin D treated CD patients from 19% (range 10 - 39%) to 29% (11 - 79%) (p = 0.03) compared with placebo-treated patients. Vitamin D treatment, but not placebo, decreased the expression of the T cell activation marker CD69 from 42% (31 - 62%) to 33% (19 - 54%) (p = 0.01).
Karimi et al-[25]	2019	50	Role of two VIT D regimens in UC and Crohn's disease.	Results indicate the 2000IU daily dose of VIT D can increase its concentration and quality of life while reducing disease activity
sharifi A-[26]	2019	90	90 mild-to-moderate UC patients were	Compared to placebo, vitamin D had significant decreasing effects

			assigned to get either a single muscular injection of 7.5 mg vitamin D3 or 1 mL normal saline as placebo. Three months later serum levels of IL-4, IL-10, IL-12p70, IFN-γ, and TNF-α were measured.	on serum TNF-α, IFN-γ, and IL12p70 levels, but it had no significant effect on serum levels of IL4 and IL10. Suggesting a therapeutic modulatory effect of VIT D
Mayur Garg et al – [27]	2018	5	5 patients with low VIT D - IBD patients are treated with VIT D and watched for the results	A specified oral vitamin D regimen successfully and safely achieved target or near-target levels, improved symptom-based activity scores, but did not alter objective measures of intestinal or systemic inflammation.

AUTHOR OF STUDY	YEAR OF PUBLICATION	NO OF SUBJECTS INVOLVED	FOCUSED SUB-TOPC	STUDY RESULTS
Zhao J et al. [17]	2019	65 - UC, 50 - Crohn's disease	Serum vitamin D levels were detected and compared between groups and among patients with different disease activity.	Patients with severe disease had even lower serum vitamin D than those with mild disease. Since patients with IBD have vitamin D deficiency, vitamin D supplementation should be investigated as a potential treatment for patients with IBD
Gubatan J [18]	2021	60	If the vitamin D is associated with α4β7 immunophenotypes and risk of vedolizumab [anti-α4β7] failure in IBD.	serum 25[OH]D is inversely associated with α4β7 expression on PBMCs and intestinal leukocytes, that VDR is inversely associated with mucosal gene expression of ITGA4 and ITGB7, and that low serum 25[OH]D is associated with increased risk of future vedolizumab failure among patients with IBD.
Lin X [19]	2023	50	T helper 17/T-regulatory cell level, inflammatory indicators, and nutritional status were compared between the 2 groups [Routine treatment grp vs VIT D added grp] , as well as mucosal healing under endoscopy and the life quality of patients.	Vitamin D has the potential to improve the inflammatory status and immune environment of patients with Crohn's disease, which can reduce the level of inflammatory factors and help the recovery of symptoms, thus improving the clinical course and quality of life in Crohn's disease patients.
Zhu C [20]	2022	Unknown	**To** investigate the immunomodulatory	Vitamin D might have anti-inflammatory potential in the

			effects of vitamin D against the UC, and to explore the potential downstream mechanisms.	treatment of the UC.
Gao H [21]	2022	30	Vitamin D3 alleviates inflammation in ulcerative colitis	Vit D3 alleviates inflammation in Ulcerative colitis by activating the VDRL-NLRP6 signalling pathway
Jinzhong Li et al [22]	2018	Eighteen RCTs involved 908 patients were included	purpose of this meta-analysis is to evaluate the therapeutic effect and safety of VitD in the treatment of IBD.	VitD reduced the relapse rate more significantly than the control group, but there were no significant differences between the low-dose and high-dose vitamin D treatment. The erythrocyte sedimentation rate (ESR) and high-sensitivity C-reactive protein (hsCRP) of the VitDand the control group showed no statistically significant difference

Effects of providing vitamin D in IBD

The research mentioned above demonstrate that there is a link between VIT D and IBD. Regular supplementation with vitamin D has been shown to reduce disease severity. If not the main nutritional supplement, it can be used as an additional therapy. According to BINCY et al. [23], patients taking vedolizumab for both UC and CD had higher pre-treatment vitamin D levels, which was related with greater endoscopic improvement of disease severity. A comparable trial by Mayur Garg et al. [27] found that adding 5000 to 10,000 international units per day of vitamin D in people with active inflammatory bowel disease for 12 weeks reduced clinical symptoms. Mayur Garg et al. [27]. It was also discovered that the medication did not cause major side events while continuously decreasing the activity index and regulating recurrence via CDAI for Crohn's disease and HBI for ulcerative colitis.

Conclusion:-

In conclusion, our review underlines the importance of vitamin D incontrolling the innate immune response in the intestines, as well as the possibility of supplementing with vitamin D in managing numerous diseases while maintaining intestinal immune response homeostasis. It has a number of pleiotropic effects that may be useful in both the prevention and treatment of IBD, including anti-infective, anti-inflammatory, and immunomodulatory properties, as well as the maintenance of gastrointestinal barrier integrity and healthy gut microbiota composition. Evidence suggests that vitamin D administration can significantly lower inflammatory inflammation in the gut. Clinical trials are required to discover the best therapy regimen, including optimal target serum vitamin D concentrations, forms, dosages, and treatment methods.

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