The valuable role of vitamin D and calcium in prevention of colorectal carcinoma

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Abstract

Colorectal cancer is a major cause of cancer mortality in the developed country. Diet and nutrition are estimated to interpret 30-50% of the colorectal cancer incidences. A possible protective effect of vitamin D and calcium against colorectal carcinogenesis has been suggested. Many studies reported that individuals with both higher supplemental and dietary intake of vitamin D, calcium or both and high plasma levels of vitamin D, have a significantly reduction in the risk for developing colorectal cancer mortality. However, the administration of supra physiologic concentrations of calcitriol leads to development of hypercalcemia. Another study found that the daily supplementation of vitamin D with calcium for seven years had no effect on the incidence of colorectal cancer among postmenopausal women. Other trial for the prevention of colorectal adenomas found that the daily supplementation with calcium, vitamin D3 or both after removal of colorectal adenomas did not significantly reduce the recurrent risk of colorectal adenomas. Many mechanisms prove the roles of vitamin D and calcium as colorectal anticarcinogens. Also, epidemiological studies and clinical trials of vitamin D and calcium supplementation on CRC risk support this role. However, their optimal forms and appropriate concentrations should be established. The Objectives of this study is To update our knowledge about the role of vitamin D and calcium in prevention of colorectal cancer and its mechanism.

Index Terms: Colorectal cancer, vitamin D, calcium, prevention, supplementation, carcinoma, prevalence.

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INTRODUCTION:

Colorectal carcinoma is a cancer that being in the colon or the rectum [1]. It is a major cause of cancer mortality in the developed country [2]. It being the third diagnostic cancer among male and the second among female worldwide [3]. Meanwhile, in Saudi Arabia, this cancer is the first in male and the third in female [4]. Nutritional factors are considered to have a serious role in its risk [5]. Nutrition and diet are evaluated to explain 30-50% of the colorectal cancer incidences [6]. A potential protective action of calcium and vitamin D with colorectal cancer has been proposed from outcome of many studies [7,8]. Several mechanisms have been suggested to demonstrate the roles of calcium and vitamin D as colorectal anticarcinogens including binding of long chain fatty acids and bile acids in the small intestine, thereby protecting colonic epithelial cells from mutagens, as well as effects on cell-cycle regulation, cell proliferation and differentiation, angiogenesis and apoptosis [7, 8-12]. On the other side, some studies don't support a protection role of vitamin D and calcium intakes against CRC [13,14]. I choose this topic because the incidence of CRC is increasing, and we should find way to prevent it. The objectives of this study are to update our knowledge about the role of vitamin D and calcium in prevention of CRC and its mechanism.

REVIEW OF LITERATURE:

1. COLORECTAL CANCER

Colorectal cancer (CRC) is a cancer that starts in the cells of colon or rectum [1].

1.1 PREVALENCE

In the worldwide, the third most common cancer among males is CRC (746,000 cases) and it is the second among females (614,000 cases). About 55% of the cases occur in more industrialized areas [3].

Moreover, this cancer in Saudi Arabia population is the first in men and the third in women. It affected 541 (52.4%) males and 492 (47.6 %) females [4].

1.2 AGE

The incidence of CRC and its death rate are increasing with age according to American Cancer Society. There are 90% of new cases and even more 93% of deaths occur with age 50 or older. The Average age at colon cancer diagnosis, 69 years old in men and 73 years old in women, is older than the median age at rectal cancer diagnosis, which is 63 years old in men and 65 old in women [15].

1.3 RISK FACTORS

The most risk factors of CRC are the modifiable factors, which include alcohol intake, consumption of processed and red meat, obesity and smoking. However, there is a positive association of non-modifiable factors which include the age, the family history of CRC and inflammatory bowel disease [16].

1.4 PATHOGENESIS

CRC is a cancer that originates from the epithelium cells padding the colon or rectum, most frequently due to mutations in the pathway of Wnt signaling which raise signaling activity. This mutation can be acquired or

inherited, most possibly happen in the intestinal crypt stem cell. The generality usually mutated gene in all CRC is the APC gene which is product the APC protein. The APC protein inhibits β-catenin protein accumulation. Without APC protein β-catenin will accumulate to high levels then moves to nucleus binds DNA, and activates the transcription of the proto-oncogenes. These genes are typically essential for stem cell differentiation and renewal, but when they unsuitably expressed at high levels they can lead to cancer. In most colon cancers the APC is mutated, some cancers have β-catenin in high levels as a result of mutation in β-catenin (CTNNB1) that will prevent its own breakdown or have other mutations in some genes which have an analogous function to APC [17].

2. VITAMIN D METABOLISM

Vitamin D is a fat-soluble vitamin that is found in some foods or it is obtainable as a dietary supplementation. It is also formed endogenously when the ultraviolet rays of sunlight fall in the skin and excite vitamin D synthesis [18].

Vitamin D gained from food, sun exposition and supplementation is biologically inactive and must have two more hydroxyl groups for activation in our body [19]. The first hydroxylation happens in the liver and transformation of vitamin D to 25-hydroxyvitamin D [25(OH)D] also known as calcidiol by an enzyme called vitamin D-25hydroxylase (predominantly CYP2R1). The second hydroxylation happens in the kidney and produces the physiologically active form 1,25-dihydroxyvitamin D [1,25(OH)2D] also known as calcitriol by the cytochrome P450 enzyme CYP27B1 (1α-hydroxylase) [20].

The CYP24A1 or 24-hydroxylase, is induced by calcitriol and it is important as it encodes the enzyme which catalyzes the degradation of 25(OH)D and 1,25(OH)2D. The action of the hormone is self-regulatory because it concurrently encourages its own inactivation [21].

2.1 VITAMIN D ACTIVITY

Calcitriol acts by binding to and activating the nuclear vitamin D receptor (VDR), which is a one of the steroid–thyroid–retinoid receptor superfamily of ligand-activated transcription factors. VDR is found in most of cells of our body, and calcitriol straight or in straight regulates as 3% to 5% of our human genome [22-24].

Vitamin D beside its role as a regulator of calcium and phosphorus metabolism at target tissues, it can modify the defenses in the body [22]. It can hinder the development of many diseases including cancer [25-27].

Though, the kidney is the main origin of circulating calcitriol, CYP27B1 is also expressed in many extrarenal sites, like cancer cells, where it can exert anticarcinogens activity [28]. Calcitriol can function in an autocrine, intracrine, endocrine or paracrine manner when it is locally synthesized. In comparison to the renal enzyme, calciotropic hormones will not regulate extrarenal CYP27B1.The existence of CYP27B1 in cancer cells indicate that dietary vitamin D may be used in cancer treatment to exert anticarcinogens effects. However, the administration of supra physiologic concentrations of calcitriol leads to development of hypercalcemia, due to the activity of calcitriol in stimulating the intestinal calcium absorption. Research efforts militate to develop a calcitriol analog with anticarcinogens effect but minimal hypercalcemia [27-29].

2.2 ANTICANCER EFFECTS OF VITAMIN D

2.2.1 CYP24A1 AND CYP27B1 EXPRESSION IN CANCER

A high basal expression rate of the enzyme CYP24A1 happen in different cancer cells making them have calcitriol-resistant actions [27]. Instantaneous upregulation of CYP24A1 is occurred in some cancers, which associates with poor clinical result. Inhibition of CYP24A1 function amplifies the biological action of calcitriol; actually, by the use of cytochrome P450 inhibitors, such as liarozole, ketoconazole and genistein, raise the biological activity of calcitriol, and can lead to calcitriol-resistant cells to return to sensitive cells [30]. Genistein exists in raisins (1458 mg), currants (2167 mg), plums (550 mg), prunes (661 mg), passion fruit (403 mg), strawberries (457 mg), soy products (100 mg) and mango. Moreover, the integration with CYP24A1 inhibitors raise the anticancer activity of calcitriol and rise the risk of hypercalcemia. Moreover, a careful approach is indispensable while using these combination [27]. Information on CYP27B1 expression and action in cancer are more diverse [31]. Its regulation in cancer cells may rely on the tumor stage, tissue and the stage of cellular differentiation, being greater in well differentiated tumors and poorly in differentiated tumors. [27].

2.2.2 ANTIPROLIFERATIVE EFFECTS BY CALCITRIOL

Calcitriol has an immediate antiproliferative activity on tumor-derived endothelial cells by inhibiting the mitogenic signaling by growth factors, like IGF-1, increasing the expression of epidermal growth factor, IGF-1 binding protein and a raise in growth inhibitors like TGF-β. It increases the expression of cyclin-dependent kinase (CDK) inhibitors p27 and p21, decreasing CDK action and arresting the cell cycle. It initiates apoptosis through activation of its intrinsic pathways and by suppression of apoptosis-specific genes like BCL-2 [27], cell-specific pro-differentiation mechanisms like regulation of β catenin, NFκB signaling pathways and JUN N-terminal kinase [32]. It inhibits angiogenesis through suppression of the expression of vascular endothelial growth factor (VEGF) by transcriptional repression of hypoxia-inducible factor 1 alpha (HIF1α) and IL-8 in an NF-κB–dependent manner. VDR null mice have

increased expression of pro-angiogenic factors like VEGF, angiopoietin, HIF1α and platelet-derived growth factor (PDGF) in tumors. Calcitriol has anti-inflammatory activity in suppressing prostaglandin and cyclooxygenase 2 (COX-2) [33].

2.2.3 INHIBITION OF WNT SIGNALING BY VITAMIN D

As the mutations in the tumor suppressor APC, or less frequent in β-catenin or Axin occurs in over 90% of colon cancers; the oncogenic Wnt/β-catenin signaling pathway is abnormally activated [34]. 1,25D3 has been reported, in a VDR-dependent manner, to oppose Wnt signaling through many mechanisms. These involve sequestration of β-catenin through an immediate VDR/β-catenin interaction and induction of the nuclear export of β-catenin. It also promotes the expression of cystatin D and DKK1, which are endogenous inhibitory of Wnt signaling and also the expression of its target genes, like Snail. Cystatin D inhibits immigration and anchorage- independent growth of cancer cells in colon and its silencing rescind the anti-proliferative action of 1,25D3 and raise the expression of c-Myc [35].

2.2.4 ANTI-INFLAMMATORY PROPERTIES OF VITAMIN D

It has been determined that cancer and different chronic diseases are linked to para-inflammation, a minimum degree of inflammation that is connected to a constant activation response of the DNA destruction [36].

It has been reported that the constant use of nonsteroidal anti-inflammatory drugs (NSAIDs) inhibits adenomas in familial adenomatous polyposis (FAP) patients, who inherit a mutation in the APC gene and minimize the mortality from CRC [37].

Diet-induce obesity is a risk factor for colorectal cancer; it is also connected with an increase in the expression of tumor necrosis factor-beta (TNF-β) in the intestine. TNF-β has also been linked to inactivation of glycogen synthase kinase 3 beta (GSK3-β) and raised expression of c-Myc and β-catenin, indicating that obesity increases colorectal cancer risk by promoting inflammation [38]. In fact, western style diet (WSD), adequate to start intestinal tumorigenesis in mice, has been shown for triggering an inflammatory response in mice, escorted by macrophages cumulation in intestinal mucosa and increase in the levels of circulating proinflammatory cytokines, like CCL2, CCL5 and IL-1β. Consequentially, dietary supplementation with Ca and vitamin D prohibit WSD-encourage raise in inflammatory markers and decreases intestinal tumorigenesis [36,37]. Dietary supplement with 1,25D3 reduced markers of inflammation like IL-1β, IL-6, IL-8, TNF and C-reactive protein (CRP) in colon cancer patients, highly propose that 1,25D3 have protective from colon cancer by decreasing inflammation [37].

2.3 ROLE OF VITAMIN D RECEPTOR AS AN INTESTINAL BILE ACID SENSOR

It has reported that VDR functions like intestine bile acid sensor. Lamprecht and Lipkin [7] demonstrated that the activated VDR by potentially toxic lithocholic acid (LCA), that is recognized to elevate colon carcinogenesis, initiates the expression of cytochrome P450, family 3, subfamily A (CYP3A) to detoxify LCA in the intestine and liver.

Particularly, CYP3A gene is a target of vitamin D in the intestine. By binding to VDR, subsequently, LCA may activate a feedback mechanism that ends in its own degradation. The protected effect provided by VDR against LCA may be overcome when the detoxification pathway is filled e.g. by raise the levels of LCA provide by WSD that are high in fat [7].

2.4 SUNLIGHT AND VITAMIN D REDUCE THE LIKELIHOOD OF COLON CANCER

It is suggested that vitamin D is a protective agent against CRC. This hypothesis arises from the search of the geographic distribution of CRC deaths in the US, which detected that CRC mortality rates were elevated in places where populations were exposed to the lower amounts of sun light [38].

2.5 CLINICAL TRIALS OF VITAMIN D SUPPLEMENTATION ON CRC RISK

Many prospective studies reported that individuals with high plasma levels of total 25(OH)D have a significant reduction in the risk of CRC compared to those have low plasma levels [40,39].

In a meta-analysis which included five epidemiologic studies, found that individuals with serum 25(OH)D level ≥33 ng/mL had a 50% decrease risk of CRC compared to individuals with levels ≤12 ng/mL ($P<0.01$) [41].

Also, a meta-analysis which included 18 prospective studies reported that individuals with both higher supplemental and dietary intake of vitamin D and high plasma levels of 25(OH)D, have a significantly reduction in the risk for developing CRC [42].

Consistent with these findings, a report from the Third National Health and Nutrition Examination Survey proved an inverse relationship between CRC mortality and serum 25(OH)D levels and, with levels 32 ng/mL or more is connected with a 72% risk decrease (95% CI,32% -89) compared to levels <20 ng/mL (P trend=0.02) [43].

One five-year study of 120,000 people reported that men with the highest vitamin D intakes had a risk of CRC that was 29% less than men with decrease vitamin D intakes [44].

A randomized control trial estimated the combination of calcium 1,400–1,500 mg/day + vitamin D 1,100 IU/day versus placebo versus calcium alone in 1,179 post-menopausal healthy women living in Nebraska, proved a 60% decrease in all cancer risk including CRC [45].

3. CALCIUM

Calcium is one of the most important mineral in the body. It is found in some foods also existent in some medicines (like antacids) and available as dietary supplement. It is demand for muscle function, vascular contraction/dilation, intracellular signaling, hormonal secretion and nerve transmission, although less than 1% of total body calcium is necessary to support these metabolic functions [46].

3.1 ROLE OF CALCIUM IN CRC PROTECTION

There is persuasive laboratory evidence that reported calcium role in reducing the risk of CRC. The reactive oxygen species (ROS) play a definitive role in start apoptosis in cancer cells. Many studies have explained already that troubled cellular calcium homeostasis has been involved in cell apoptosis. They reported that an ROS rise lead to death of cancer cells caused by mitochondrial calcium effort and that calcium-dependent ROS is a signal molecule that could stop proliferation of cancer cell in human colon cell culture [47]. The calcium-sensing receptor (CaR) may work like a transmission to change on and change off cancer cells. In numerous cell types, such as epithelial cells of the intestine, by working onto these receptors, extracellular calcium concentricity can change the cellular demeanor from proliferation to terminal quiescence or differentiation [48]. A considerable quantity of evidence showed that calcium has an immediate role in growth-restraining, apoptosis and differentiation -inducing activity on normal and tumor cells, including cells of the gastrointestinal tract. An antiproliferative activity of dietary calcium on cell of the intestine also outcome due to binding to fatty and bile acids, that may minimize the possibility of destructive, proliferation-encourage effects of these composition on the intestine mucosa [7].

3.2 CLINICAL TRIALS OF CALCIUM SUPPLEMENTATION ON CRC RISK

A comprehensive retrospective review including 1,346 persons using diverse various research engines complemented that even though the evidence from two randomized controlled trial (RCT) found that calcium supplementation may give a mild grade to the prevent of colorectal adenomatous polyps, this did not form enough evidence to advise the general use of calcium supplementation may prevent colorectal cancer[49].

A study including 930 patients with a recent CRC was intended to check the action of calcium on various types of colorectal lesions. Patients were randomly assigned to placebo or 1,200 mg/d calcium carbonate. Follow-up colonoscopies were performed approximately one and four years after the qualifying examination. The outcome propose that calcium supplement might have a more clear antineoplastic action on advanced colorectal lesions than on another types of polyps [50].

4. STUDIES THAT DON'T SUPPORT THE ROLE OF VITAMIN D AND CALCIUM SUPPLEMENTATION IN CRC INCIDENCE

A RCT including 36,282 postmenopausal women from 40 Women's Health Initiative centers found that the daily supplementation of vitamin D with calcium for seven years had not shown any effect on the incidence of CRC [13].

Other trial of vitamin D and calcium for the prevention of colorectal adenomas found that the daily supplementation with calcium (1200 mg), vitamin D3 or both together after remove of colorectal adenomas did not markedly minimize the risk of recurrent of colorectal adenomas from 3 to 5 years [14].

CONCLUSION:

Vitamin D and calcium have been suggested to have potential protective effects against colorectal carcinogenesis. Many mechanisms demonstrate the roles of them as colorectal anticarcinogens. Also, epidemiological studies and clinical trials of vitamin D and calcium supplement on CRC risk support this role.

The optimum forms and appropriate concentration of vitamin D and calcium that have cancer prevention action should be confirmed, and RCT are necessary to prove the role of vitamin D and calcium.

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