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REVIEW ARTICLE

The Physiological/Pathophysiological Significance of Vitamin D in Cancer, Cardiovascular Disorders and Beyond

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Abstract: Vitamin D, a molecular precursor of the potent steroid hormone calcitriol, has crucial functions and roles in physiology and pathophysiology. Tellingly, calcitriol has been shown to regulate various cellular signalling networks and cascades that have crucial role in cancer biology and diagnostics. Mounting lines of evidences from previous clinical and preclinical investigations indicate that the deficiency of vitamin D may contribute to the carcinogenesis risk. Concomitantly, recent reports suggested that significant reduction in the cancer occurrence and progression is more likely to appear after vitamin D supplementation. Furthermore, a pivotal role functioned by vitamin D in cardiovascular physiology indicates that the deficiency of vitamin D is significantly correlated with enhanced prevalence of stroke, hypertension and myocardial infarction. Notably, vitamin D status is more likely to be used as a lifestyle biomarker, since poor and unhealthy lifestyles are correlated with the deficiency of vitamin D, a feature which may result in cardiovascular complications. Moreover, recent reports revealed that the effect of vitamin D is to cover not only cardiovascular system but also skeletal system. Of note, the correlation between vitamin D deficiencies with rheumatoid arthritis (RA) progression might suggest a pivotal role of vitamin D in either initiation or progression of the disease. Herein, we are highlighting the recent knowledge of vitamin D roles and functions with respect to pathophysiological disorders such as cancer, cardiovascular diseases, rheumatoid arthritis (RA) and debate the potential avails of vitamin D on slowing cancer, cardiovascular disease and RA progression.

Keyword: Vitamin D, cancer, cardiovascular diseases, rheumatoid arthritis (RA), clinical trials, therapeutic agent.

INTRODUCTION

Vitamin D is biochemically obtained from three major molecular routes, cholecalciferol, an unhydroxylated and inactive format of vitamin D3, ergocalciferol or vitamin D2, which is considered as an active fungus-derived molecule, and the endogenous synthesis from 7 dehydrocholesterol in the skin upon exposure to the sunlight [1]. However, remarkably, due to various life factors that include the increase in indoor occupation; the increase in avoidance of sunlight, many people suffer from poor exposure to the proper amount of sunlight [2]. As a result, a huge number of individuals globally have suffered from the deficiency of vitamin D [2]. Notably, the deficiency of vitamin D has been documented to be prevalent in children and young adults and elderly men and women [3-6]. Several pathophysiological disorders have been mediated by vitamin D deficiency. Previous investigations have unveiled the linkage between the deficiency of vitamin D and impaired bone health [7, 8]. In a previous report, 25[OH] D3 ≤75 nmol/l has revealed to be affiliated with enhanced risk of hypertension, respiratory disorders, peripheral vascular diseases and diabetes [9, 10]. With the finding that vitamin D receptor (VDR) is recognised in almost all tissues and the recent discovery of many of VDR binding sites and their potential critical roles in cellular physiology, the interest in vitamin D and its impact on multiple cellular signalling processes have expanded largely as evidenced by the exponential growth in number of publications each year for the past several years within the field [11]. The recent structural, biochemical and chemical advances in vitamin D receptor characterization lead to increasing the effort to develop vitamin D analogs which can functionally differentiate the bio -effects of the metabolite 1,25-dihydroxyvitamin D (1,25(OH) 2D) on phosphate and calcium homeostasis from its other cellular and biological effects [12]. For instance, calcipotriol and 22-oxa calcitriol (OCT) have been approved for the treatment of psoriasis. Paricalcitol, doxercalciferol, and falecalcitriol have been approved for secondary hyperparathyroidism (OCT and falecalcitriol are approved for use only in Japan) [13]. The molecular mechanisms by which these analogs attain specificity for these therapeutic applications have been attributed to several reasons that include:1- their relative specific affinity for the major vitamin D transporter protein in blood (vitamin D binding protein [DBP]), 2- their metabolism either as prodrug activation or rates of catabolism, 3- their affinity for the VDR and their ability to affect the transcription of VDR via molecular effects on the heterodimerization of retinoid X receptor [14]. Thus, given the central significance of vitamin D in diverse biological processes and its clinical applications, it is essential to further improve our understanding about different aspects of vitamin D mechanisms of action and metabolism that can be modulated to facilitate tissue-specific clinical applications [14]. Herein, we discussed implications and uses of vitamin D in different kinds of diseases and disorders.

VITAMIN D SYNTHESIS AND GENERATION

The process of generation of vitamin D3 (D3) in the skin is depicted in (Fig. **1**). Vitamin D3 (cholecalciferol) is generated from

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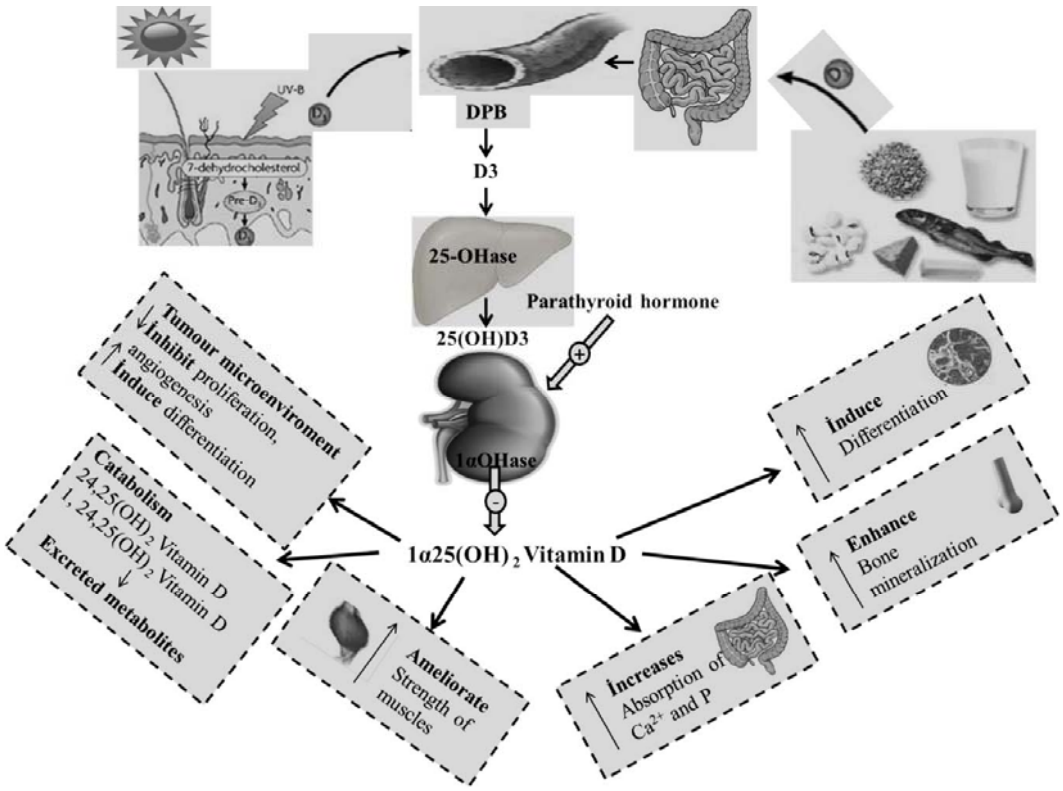

Fig. (1). The generation and metabolism of D2 and D3.

7-dehydrocholesterol (7-DHC) via a two-step process through which the B ring is spilt via UV light (spectrum 280–320 UVB) radiation from the sun generating pre-D3 that subsequently isomerizes to D3 in a thermo-sensitive process. Both skin pigmentation and UVB intensity contribute to the rate of D3 generation [15]. The pigment melanin in the skin plays an important role in this process by blocking UVB from reaching 7-DHC, thus restricting D3 generation, as sunscreen and some clothing pattern. The levels of UVB from sunlight varies with respect to a number of factors as latitude and season, therefore the further one resides away from the equator, the less time one need to expose solar rays to generate D3 [16]. Vitamin D may also be provided through the diet. Notably, the vitamin D in fish is D3, while the one that is often used for fortification is D2 (ergocalciferol). D2 is generated by UVB irradiation rays of the ergosterol in plants and fungi (e.g., mushrooms). It differs chemically from D3 in that it has a double bond between C22 and C23 and a methyl group at C24 in the side chain. Consequently, D2 can be considered the first vitamin D analog. These differences from D3 in the side chain dampen its affinity for DBP resulting in faster clearance from the circulation, restrict its biochemical conversion to 25 hydroxyvitamin D (25OHD) by some of the 25-hydroxylases, and change its catabolism rate by the 24-hydroxyase (CYP24A1) [17-19]. Thus, unless given daily, D2 supplementation does not result in as high a blood level of 25OHD as comparable amounts of D3 [20]. Noteworthy, 1,25(OH)2D2 and 1,25(OH)2D3 have approximate similar affinities for the VDR [18].

METABOLISM OF VITAMIN D

The three major steps of vitamin D metabolism, which are 25-hydroxylation, 1a- hydroxylation, and 24-hydroxylation, are mediated by cytochrome P450 oxidases (CYPs). The localization of these enzymatic reactions is either in the endoplasmic reticulum (ER) (e.g., CYP2R1) or in the mitochondria (e.g., CYP27A1, CYP27B1, and CYP24A1). Of note, the reduced nicotinamide adenine dinucleotide phosphate (NADPH)-dependent P450 reductase acts as the source for electrons for the ER enzymes. The electron donor chain for the mitochondrial enzymes includes ferredoxin and ferredoxin reductase. While these are not specific for a given CYP, biochemical specificity lies within the CYP. Although the contribution of CYPs in vitamin D metabolism, just two enzymes CYP2R1 and CYP24A1 have been crystallised, it is more likely that these enzymes bears a number of common structural features. These include 12 helices (A–L) and loops and a common prosthetic group, particularly the iron-containing protoporphyrin IX (heme) linked to the thiolate of cysteine. The I helix passes via the center of the enzyme above the heme where a thr(ser) and asp(glu) pair are crucial for the catalytic activity. CYP2R1, similar to other microsomal CYPs, contains two extra helices that are critical for the formation of a substrate channel in the bilayer of the ER [21]. Tellingly, The B0 helix acts as a gate, closing on the substrate binding. It is still unclear if a similar substrate channel exists for the mitochondrial CYPs [14].

VITAMIN D MECHANISM OF ACTION

Vitamin D exerts some gene expression roles through transcriptional activities via the transcription factor VDR [22-23]. VDR is a transcription factor and is from one of the steroid hormone nuclear receptor families. Its modular structure involves three areas: the N-terminal area with two zinc fingers connecting to the DNA ridges at unique sites (VDREs), the C-terminal domain binds to ligand, and a joint area which bridges these two spheres. Notably, the ligand binding domain which structure has been characterised by x- ray crystallography [24]. It consists of 12 helices. The terminal helix acts as a gating mechanism closing around the bound ligand and providing an interface for co-activators as well as making it feasible for the interaction of VDR with its heterodimer partner, particularly RXR. Despite the fact that there is significant variance in the sequence of VDREs, most of the nucleotides with significant high affinity for VDR are direct repeats of hexanucleotides with a spacer of 3nucleotides between the half sites, a sequence motif called DR3. The binding of VDR to its VDRE then recruits co-regulatory protein complexes that are crucial for its transcriptional activity.

These complexes have been shown to be gene and cell type-dependent. These complexes involve multi-subunit that have multi-functions, and include a subunit that directly binds to the VDR basically through an LXXLL motif with a number of subunits that contain enzyme catalytic activity such as histone acetyl transferases (co-activators such as the SRC family) or deacetylases (co-repressors such as SMRT and NCoR), methyl-transferases and de-methylases. The advancement in biological and biomedical laboratory techniques such as microarray, ChIP-chip, and ChIP-seq has remarkably expanded our knowledge of vitamin D molecular mechanisms of action at the molecular level and gene level. For instance, in the mouse osteoblast cells, 1,200 VDR binding sites were found upon basal cellular (i.e., no 1,25(OH)2D) conditions, while around 8,000 sites were examined upon 1,25(OH)2D administration [25]. In another report with human lymphoblastoid cell lines treated with 1,25(OH)2D, 2,776 VDR binding sites were found altering the expression of 229 genes [26]. The profile of VDR binding sites and genes activated varies from cell to cell particularly when comparing the obtained results with different time courses of 1,25(OH)2D exposure [27]. Furthermore, these VDR binding sites can be localised in any genomic loci, and interestingly many thousands of base pairs are often found far from the target gene. These sites were shown to be associated with binding sites for other transcription factors. In osteoblast cells, these include RUNX2, C/EBPa, and C/EBPb, among others [28, 29]. These DNA binding loci usually demonstrate a unique epigenetic histone signature involving methylation and/or acetylation of lysines within H3 and H4 [30]. In a recent review [22], it was highlighted that there may be six rules of VDR/RXR activity on marked genomes: 1) the amount of VDR connecting areas on the genome is dependent on the type of cell; 2) the dynamic format of transcription principally comprises the VDR/RXR heterodimer; 3) VDR linking areas are, in general terms, classic hexamer half-sites isolated by three fundamental pairs; 4) DNA augmenters may be localised near the promoter, or far away from promoter or a mixture, with respect for transcriptional start regions, and numerous enhancer elements are positioned within groups many kilobases away from their marked genes; 5) enhancers may contain linking areas for several varying transcription elements; 6) enhancers which inhabit a genome are specific to cell type and comprise dynamic form.

CLINICAL APPLICATION

Anticancer Actions of Vitamin D

Vitamin D3 is biochemically stimulated to its strong hormonal state, calcitriol, via two cytochrome P450-mediated hydroxylation reactions [31]. The initial hydroxylation stage mainly takes place within the liver at C25 producing 25-hydroxvitamin D3 (25 (OH) D3), which is catalytically mediated through vitamin D-25-hydroxylase (predominantly CYP2R1) [32]. 25(OH) D3 comprises the distributed state of the hormone which can be monitored within the blood and clinically employed to determine vitamin D grade of a patient. Circulating 25(OH) D3 is hydroxylated within the kidney on the C1α position by the cytochrome P450 enzyme CYP27B1 to generate calcitriol [33, 34]. Calcitriol mediates its cellular actions via connecting to and stimulating the nuclear vitamin D receptor (VDR), which comprises a potent transcription factor. Due to the VDR being available in the majority of cells within the body [35] and because calcitriol can control around 3–5% of the human genome, vitamin D operation is extensive, and it applies actions which may change the immune system of the body [36-39] which may apparently restrict the advancement of several diseases, such as cancer development [2, 40-52]. One of the numerous genes which are altered through calcitriol, CYP24A1 (referred to as 24-hydroxylase) comprises notable importance; it expresses the enzyme which mediates the degradation of 1,25(OH) 2D3 (calcitriol) as well as 25(OH) D3 [53]. Hence, the operation of the hormone is self-controlled, as it concurrently causes its self-deactivation. One of the potential side effects of administering higher dilutions of calcitriol is hypercalcaemia, which has been attributed to the operation of calcitriol in the promotion of intestinal calcium ingestion. Thus, structural vitamin D analogues demonstrate attenuated calcaemic impacts although maintaining the equipotent or raised anti-neoplastic roles which are still sought for treatment implications [54].

Vitamin D Control of Definite Signalling Conduits which Compel Lung Cancer Growth

A number of genes that control cell development and variation are shown to be transformed within lung cancer and a number of these genes have been shown to be altered by 1,25(OH)2D3 in diverse kinds of cancer. The (EGFR), a tyrosine kinase receptor, comprises one of the most observed mutated proteins within non-small cell lung cancer; this may result in the significant overexpression of this receptor. EGFR mediates the activation of signalling conduits which bring about increase of dissemination, angiogenesis, cellular intrusion as well as evasion of apoptotic cell death, crucial processes that are essential for cancer development [55]. Notably, the EGFR -tyrosine kinase inhibitors erlotinib and gefitinib are stated to enhance the therapy of some subdivisions of non-small cell lung cancer which bear somatic alterations within the tyrosine kinase sphere of the EGFR [56]. 1,25(OH)2D3 inhibits the molecular signalling via EGFR- signalling axis within ovarian cancer cells and causes cessation of the cell sequence [57]. Further, it has been shown to mediate cessation of development caused by tyrosine kinase inhibitors within EGFR-overexpressing epidermoid carcinoma cells, as well as in non-antiproliferative levels integrated with erlotinib; it was shown to attenuate parathyroid hyperplasia [58]. This data indicates that, as in the case of vitamin D opposition available in hyperparathyroidism, reduced- dose 1,25(OH)2D3 when mixed with an EGFR inhibitor could mediate cessation of development in lung cancer cells unaffected by vitamin D. Despite the fact that there is no current data on vitamin D influencing EGFR within lung cancer cells, these reports reveal that it could be practical to investigate whether EGFR is affected by vitamin D within lung cancer cells [59]. EGFR is upstream of several important signalling pathways; this includes the RAS/RAF/mitogen stimulated protein kinase (MEK) pathway /extracellular signal regulated kinase (ERK) conduit as well as the phosphatidylinosititide 3-kinase (PI3K)/protein kinase B (AKT)/ mammalian mark of rapamycin (mTOR) signalling cascade (Fig. **2**). It was shown that the 1,25(OH)2D3 can alter several of the main pivotal molecular intermediaries concerned. For instance, the RAS genes encode guanosine triphosphate (GTP)-binding proteins which mediate their actions via the EGFR signalling cascade. KRAS is the most broadly altered RAS gene within human cancer, and it was revealed that the alteration of this gene comprises one of the more crucial stages toward lung carcinogenesis [60]. Of note, 1,25(OH)2D3 has been stated to alter RAS functional operation within leukemia cells[61]. Vitamin D aims at a number of cellular molecular pathways within cancer cells, encompassing EGFR and downstream adherents of its intracellular signalling cascade which may enhance tumour development as well as metastasis. For instance, previous work demonstrated that vitamin D3 disassembles the AKTRAF1 compound and down-regulates AKT within leukemia cells, thus stimulating the MEK/ERK pathway, resulting in cell differentiation [62]. On the other hand, VDR overexpression was shown to be independently correlated with KRAS and PI3KCA- stimulating mutations within colorectal cancer, indicating that the availability of these mutations may disturb the role of vitamin D as a chemo-preventive or chemotherapeutic molecule [63]. Liver kinase B1 (LKB1) and control in progression and DNA damage responses 1 (REDD1) comprise key adverse controllers of mTOR, a serine threonine kinase which is downstream of PI3K/AKT and indications for cell dissemination [64]. Absence of operation mutations of LKB1 have been shown to be widespread within lung cancer that may result in the overexpression of mTOR and later cell development. REDD1 was illustrated

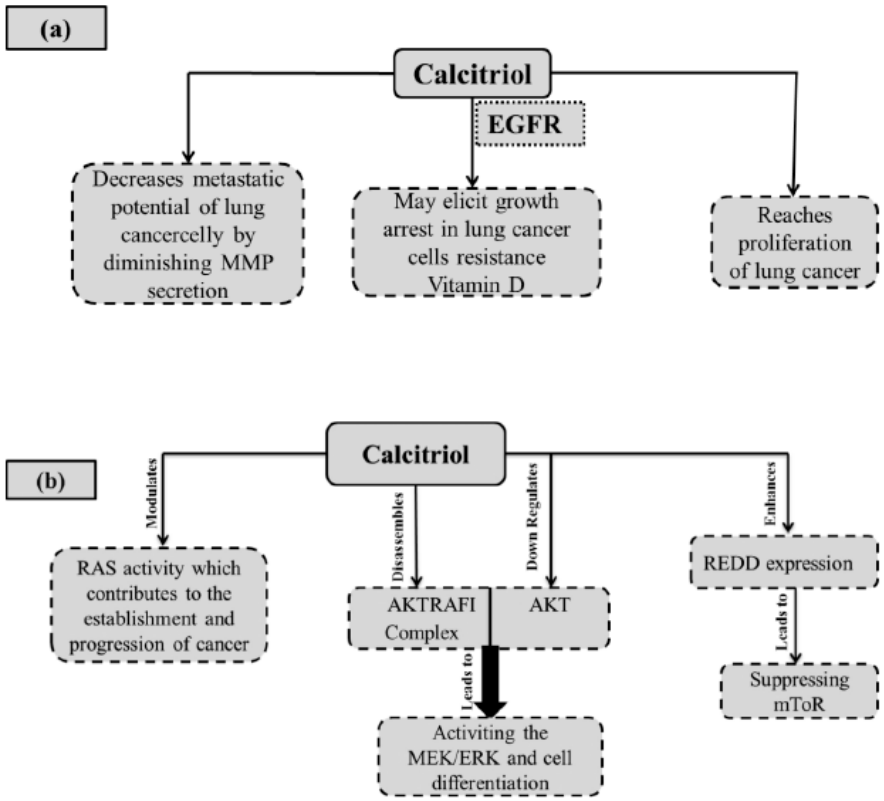

Fig. (2). The proposed action method of vitamin D in lung cancer.

to dampen the metastatic potential of lung cancer cells [65] and 1,25(OH)2D3 has lately been displayed to augment the REDD1 articulation, reducing mTOR operation within bone cells [66]. Additional exploration is essential to elucidate if this device is available in alternative cell types.

Vitamin D Effects on Signalling Pathways in Colon, Breast and Prostate Cancer

Calcitriol comprises diverse cellular and molecular roles in different kind of cancer cells (Fig. **3**). It regulates specific signalling cascades and nodes in diverse kinds of tissues such as breast, colon and prostate tissues (Fig. **4**), and hence mediates the actions of pivotal players of tumours that are present in these tissues. For example, one of the calcitriol activities within colon cancer cells is inhibiting β-catenin transcriptional function [47, 67]; this function counteracts the abnormal stimulation of WNT–β-catenin signalling, which is one of the main crucial aberrations present within sporadic colorectal cancer signalling [68]. Interestingly, the augmented SNAIL articulation within human colon cancer cells is correlated with an absence of sensitivity to calcitriol [67] that may be exploited as a diagnostic biomarker. Vitamin D3 derivatives can be exploited to modulate breast cancer signalling. For example, in postmenopausal females, when ovarian oestrogen generation pauses, local oestrogen which is generated within the breast cells microenvironment acts as major driver of oestrogen receptor-positive (ER+) breast cancer development, and adds to the control of ERα within breast cancer cells [71-74]. Most notably it has been shown that calcitriol bears a beneficial use in the avoidance or therapy of postmenopausal ER+ breast cancer. Nonetheless, several of the broad anticancer activities of vitamin D could additionally aid women having ER-negative breast cancer.

Androgens mediate the development of prostate cancer cells by means of androgen receptor (AR)- controlled signalling. Advancement of prostate cancer into castration-resistant prostate cancer (CRPC) takes place via different multiple signalling cascades, most of which are generated via AR stimulation, in spite of the castrate concentrations of androgens in the blood circulation [75-78]. Of note, a crosstalk amid calcitriol and androgen signalling cascades within several prostate cancer cells exists, which may underpin the controlled management of the expression of AR [79-81], in addition to alternative key androgen reactive genes, through calcitriol [82], control of VDR through androgens and other genes related to differentiation [83-84] and the regulation of androgen catabolism-related genes [82].

COMMON MECHANISMS OF ACTION OF CALCITRIOL

Anti-Proliferative Effects

1,25-Dihydroxyvitamin D3 (1,25-(OH)2D3), mediates the attenuation of proliferation of diverse types of cancer cells including prostate adenocarcinoma cells. Further, it has been demonstrated that 1,25-(OH)2D3 augments the half-life of the cyclin- dependent kinase inhibitor p27KIP1, reduces the cyclin-dependent kinase 2 (CDK2) operation, and augments the G1 phase buildup in prostate cancer cells. These cellular actions are associated with cytoplasmic relocalisation of CDK2 [85-88]. 1,25-(OH)2D3 mediates the increase of insulin- like growth factor binding protein 3(IGFBP-3) within the LNCaP cell line both at the transcriptional as well as posttranslational level. The development attenuation effect of 1,25-(OH)2D3 on LNCaP cells is reliant on active IGFBP-3, as indicated by the drop of development inhibition caused by IGFBP-3 siRNA or shRNA technology as well as immuno- neutralisation tests. A likely link connecting IGFBP-3 as well as 1,25-(OH)2D3 may be the cyclin reliant kinase inhibitory protein p21/WAF1, as IGFBP-3 and 1,25-(OH)2D3 can induce the up- regulation of this protein and the two can reduce the LNCaP cells development and proliferation. Thus, one possible molecular mechanism through which IGFBP-3 and 1,25-(OH)2D3 cause growth limitation comprises the inductive activation of p21/WAF1 since IGFPB-3 immuno-neutralizing antibodies can entirely abolish the 1,25-(OH)2D3- dependent up-regulation of p21/WAF1 and development reduction [89]. Upon

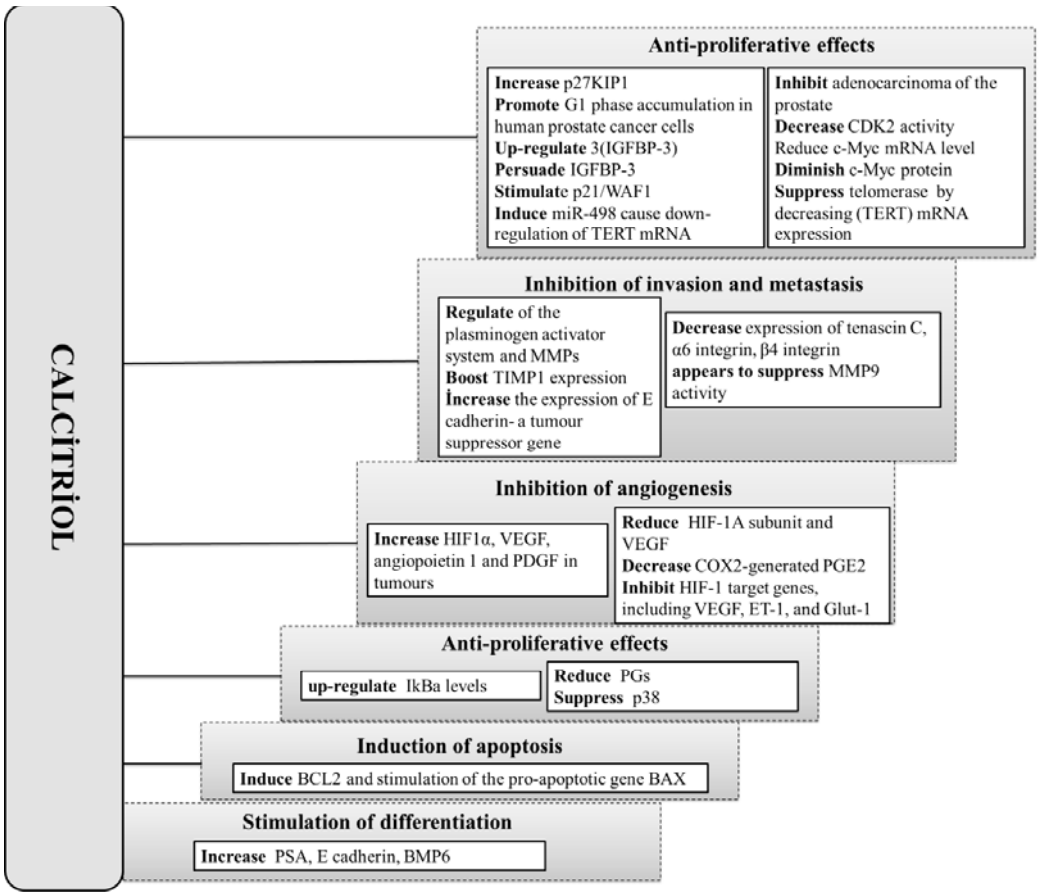

Fig. (3). Depicts the Common molecular mechanisms underlying the anti-neoplastic actions of calcitriol.

1,25(OH)2D3 treatment, a 50% lessening in c-Myc mRNA has been observed, and a more apparent reduction in c-Myc protein has been noted as well. Therapy using 1,25(OH)2D3 lessened c-Myc half-life through mediating the increase in populations of c-Myc phosphorylated on T58, a glycogen synthase kinase-3β region which acts as a site for ubiquitin-dependent protein degradation. Therefore, 1,25(OH)2D3 attenuates both c-Myc mRNA extents and c-Myc protein half-life to decrease and abrogate the growth and proliferation of prostate cancer cells [87, 90]. Furthermore, calcitriol and its molecular analogues can attenuate the relatively high telomerase operation which is observed in some cancer cells through attenuating the telomerase reverse transcriptase (TERT) mRNA expression. It has been unveiled that the introduction of miR-498 through calcitriol is involved in the attenuation of TERT mRNA in a number of cancer cells [91, 92].

Anti-Inflammatory Properties

Inflammation can contribute to the growth and advancement of several kinds of cancer [93]. Most notably, calcitriol is shown to exert anti-inflammatory roles in several cancers [42, 94]. For example, it has been demonstrated that calcitriol decreased the extents of prostaglandins (PGs), major accelerators of aromatase transcription, via subduing the articulation of cyclooxygenase-2 (that catalyses synthesis of PG) and raising that of 15 hydroxyprostaglandin dehydrogenase (that catalyses degradation of PG) [69, 95]. Calcitriol attenuates the p38 stress kinase signalling via augmenting the levels of MAPK phosphatase 5 and the subsequent reduction of pro-inflammatory cytokine generation [96]. Furthermore, calcitriol induce the increase of IkBa levels by augmenting the mRNA stability and mitigating IkBa phosphorylation. The upregulation in IkBa levels attenuate the nuclear translocation of NFkB and thus dampen its cellular activity [97-99].

Inhibition of Angiogenesis

1,25(OH)2D3 attenuates the protein articulation of both the regulated HIF-1A protein fragment and the vascular endothelial growth factor (VEGF). 1,25(OH)2D3 also mediates the decrease in the HIF-1 transcriptional activity and mitigates HIF-1 marked genes, encompassing VEGF, ET-1, and Glut-1. The containment of the hypoxia-induced VEGF by 1,25(OH)2D3 is controlled at least somewhat, via a HIF-dependent pathway and interleukin-8 (IL-8) in an NF- κB- mediated way[98, 100]. 1,25(OH)2D3 augments the articulation of pro-angiogenic mediators such as HIF1α, VEGF, angiopoietin 1 and platelet-derived growth factor (PDGF) in cancer cells. Previous work outlined that 1,25(OH)2D3 exhibits an anti-proliferative function in tumour-derived endothelial cells [101]. Interestingly, 1,25(OH)2D3 dampens COX2-generated prostaglandin E2 (PGE2), which promotes angiogenesis via augmenting HIF1α generation in cancer cells [102].

Induction of Apoptosis

Vitamin D can suppress the tumorigenic phenotype through its action on the VDR, a ligand reliant transcription element, to modulate sequences of gene articulation which subdue the neoplastic phenotype. Despite the fact that there is resemblance between the overall anti- propagative influence of 1,25D within human and mouse mammary cells, the particular marked genes controlled by vitamin D signalling differ significantly among various cellular and organismic models. Nonetheless, several cellular pathways are usually controlled by vitamin D signalling such as in the case of signalling cascades that regulate differentiation, control metabolic flux, modify the extracellular matrix and cause instinctive immune response [103]. Of note, it has been reported that calcitriol induces apoptotic cell death in several cancer cells through a mechanism

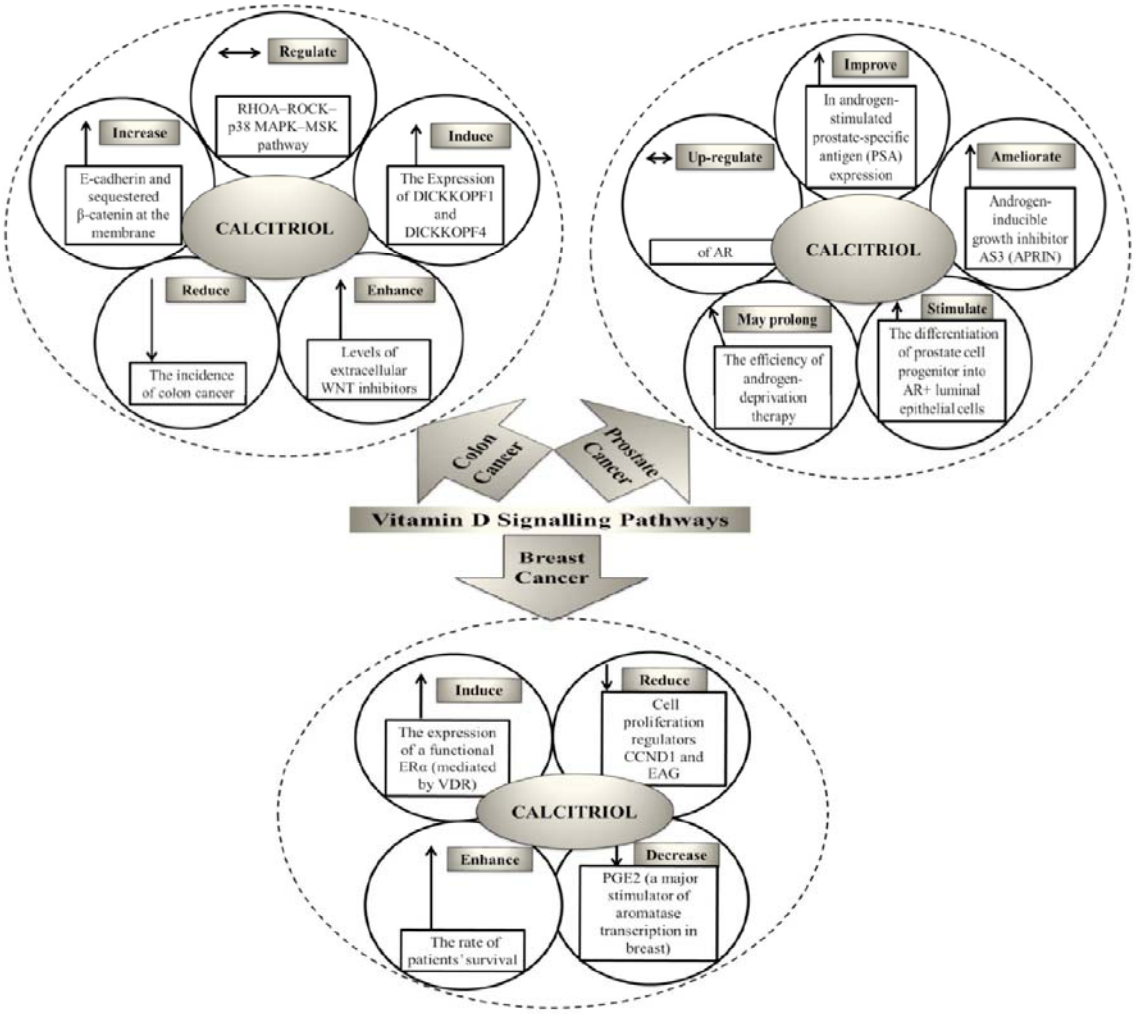

Fig. (4). Depicts the calcitriol roles that are involved in the reduction of the critical signalling pathways that compel the development of particular tumours. Such key functions encompass the restriction of the WNT–β-catenin signalling and are involved in colon cancer development, attenuation of local oestrogen production and signalling which compels oestrogen receptor- positive (ER+) postmenopausal breast cancer as well as the contact with androgen receptor (AR) signalling which induces prostate cancer.

that is largely comprised of cell type-dependent molecular mechanisms. This involves the stimulation of the intrinsic conduit of apoptosis by means of attenuation of anti-apoptotic targets like BCL2 and augmenting of the pro apoptotic member BAX [72, 104]. Prompting of differentiation.

Upon exposure to calcitriol, several cancer cells tend to exhibit a less malicious feature, and a more non-neoplastic phenotype, which implies a pro-distinguishing role [41]. Previous reported examples involve inducing the deadly separation of human myeloid leukaemia cells into monocytes and macrophages [88], the selective initiation of diversity markers like casein, lipid droplets and adhesion proteins within breast cancer cells [105], the augmented abundance of prostate-specific antigen (PSA), E-cadherin and bone morphogenetic protein 6 (BMP6) within prostate cancer cells as well as the stimulation of differentiation indicators in colon cancer cells [41].

Inhibition of Invasion and Metastasis

A previous investigation establishes a role for calcitriol in regulating the gene expression regarding the crucial players of the plasminogen activator structure as well as matrix metalloproteinases (MMPs) [106]. For instance, calcitriol mitigates the articulation of tenascin C [107], α6 integrin and β4 integrin[108]. Further, calcitriol seems to attenuate the MMP9 activity, and elevate the levels of metalloproteinase 1 (TIMP1) [109]. Calcitriol also up-regulates the levels of E-cadherin, a tumour suppressor which has inverse correlation with metastasis [110].

Clinical Trials

It has been reported that vitamin D exerts an anti-neoplastic roles in a few cancer types *in vitro* and/or *in vivo*, encompassing ovarian, prostate, pancreatic, blood, colorectal, and breast cancers [37]. A number of tests were carried out, mostly examining the effect of vitamin D in the biology of prostate cancer, despite the fact that elevated-dose 1,25(OH)2D3 employed in synergy with paclitaxel has been demonstrated to be secure for patients with prostate cancer [37, 111]. More in-depth clinical investigations are presently going on examining the 1,25(OH)2D3 cytotoxic role in prostate cancer as well as vitamin D molecular analogs in addition to small metabolites within oral, breast and colon cancer cells signalling. The possible biological role of vitamin D within the treatment or avoidance of alternative lung disorders including tuberculosis and cystic fibrosis is additionally in progress [59]. Regardless of the availability of positive pre-clinical lines of evidences from *in vitro* and *in vivo* investigations for an anti-neoplastic function of vitamin D for lung cancer therapeutic purposes, scarcity has prevailed in clinical research regarding the usage of vitamin D and its analogs for avoidance or therapy, whether singularly or in conjunc-

tions with other chemotherapeutic medications. This can be attributed to anxieties regarding vitamin D's harmfulness or lack of full understanding of its molecular mechanisms of action and it potential cellular targets in different genotypes. Previous clinical studies indicated that administering 2 μg/day of 1,25(OH)2D3 over 12 weeks in treating patients with myelodysplastic disorder resulted in no significant advantage in disease and conversely caused hypercalcemia, strongly indicating that vitamin D exhibits toxicity towards the individuals [112]. Nonetheless, another report [113] demonstrated that supplementation leading to relatively high levels of plasma 1,25(OH)2D3 (600-1440 pg/ml), mixed with paclitaxel, anti-cancer drug of taxane family that is used for lung cancer patients, result in no dose-restricting toxicity [113]. Of note, there is little experimental data regarding the utmost allowed dose and dose- restricting cytotoxicity for various cancer cell types [111]. Moreover, there are some pharmacological issues regarding whether certain regimens are capable of attaining the doses needed [111, 113]. Consequently, further study is needed for this section with suitably planned tests to examine vitamin D's role- signalling of various cancers, such as lung cancer. At present, Ramnath and colleagues [114] are investigating a stage I/II clinical test to examine the utmost accepted dose and dose- restricting poisonousness of 1,25(OH)2D3 usage in synergy with cisplatin/docetaxel in progressed non-small cell lung cancer individuals and evaluating the reaction levels. Moreover, they are investigating the correlation between systemic contact with 1,25(OH)2D3 of patients having polymorphisms within the CYP24 enzyme, which breaks down vitamin D, on systemic alterations on some particular coding areas of genes that are linked to low vitamin D catabolism [114]. The Vitamin D and OmegA-3 TriaL (VITAL) are currently under investigation to examine whether daily supplementation in diet of vitamin D3 (2000 (IU)) or omega-3 fatty acids (1 gram of fish oil) or combination of the two can attenuate the susceptibility to development of cancer, heart disease as well as stroke in individuals with no prior history of these disorders [115]. These trials may ultimately uncover new mechanistic roles of vitamin D within human cancer and alternative disorders. In another study of the Women's Health Initiative (WHI; a number of investigations of hormone substitution for postmenopausal women), it was shown that minor doses of vitamin D3 (400 IU per day) and calcium (1 g per day) result in non -substantial effect in mitigating the incidence of breast or colorectal cancer [117]. Of note, there was a rise in nephrolithiasis levels (calculi in the kidneys). Notably, it was demonstrated that the limitations of this report involved the usage of the reduced vitamin D3 dose provided to subjects (since it was shown that 400 IU causes only a minor or no increase in serum 25(OH)D levels) [118]. A re-evaluation of the vitamin D3 and calcium investigation within this RCT indicated a role of vitamin D3 in attenuating breast and colon cancer in few individuals who were allocated to get the enhancements, suggesting that even minimal doses have a likely beneficial role in females who could have had reduced commencement amounts of 25(OH)D[119]. Nonetheless, this analysis could be theory producing and should be considered cautiously [120]. An example of a clinical trial indicating the significance the combination of calcium and vitamin D3 is a 4-year osteoporosis and fracture RCT in 1,179 fit postmenopausal females who had cancer occurrence as the main secondary result [121]. The individuals were given 1,400–1,500 mg additional calcium (Ca group), supplemental calcium added to a 1,100 IU vitamin D3 (Ca +D group) or blank control each day. Cancer occurrence was reported to be reduced in the Ca division and additional reduction was observed in the Ca+D division with respect to the placebo division. Treatments as well as serum 25(OH)D intensities were significantly independent markers of cancer susceptibility. Another osteoporosis trial [122] investigated 135 incident instances of cancer and revealed no positive correlation linking interventional vitamin D3 and cancer occurrence, yet it did illustrate mitigation in colorectal cancer death rate. A colon cancer test which exploited dietary supplement of vitamin D3 (800 IU every day) and calcium (2 g every day) over 6 months in 92 individuals revealed a turnaround of biomarkers of augmented danger of colon cancer in biopsies of regular colorectal mucosa derived from individuals experiencing surgery for sporadic colorectal adenoma [123]. A large body of researches which employed vitamin D3 usually integrated it with calcium, and it is not apparent if the beneficial role were solely from the vitamin D3 or if calcium has a role too, as reported to be true for some trials [121, 123]. A new meta-analysis of eight main vitamin D3 tests, which appraised fracture occurrence in over 70,000 individuals [124], disclosed that vitamin D3 as well as calcium mitigated the danger of mortality resulting from several causes, while vitamin D3 solely did not. Three different studies [121, 123, 124] proposed that the advantages of vitamin D3 are augmented by co-dispensation of calcium, and further research is needed to clarify the molecular structure of these results. A further trial investigation exploited vitamin D3 initially in the progression of prostate cancer for 44 individuals who had low-risk disease and who employed active surveillance as opposed to prostatectomy [125].Vitamin D3 addition (4000 IU per day) over a year was reported to be secure and resulted in no negative effects. Nonetheless, on recurrent prostate biopsies following the first year, 55% of the individuals unveiled mitigated levels in the amount of positive biopsy cores or a reduction in Gleason grade of the cancer-holding biopsies, while 34% illustrated augmented levels. Of note, it was determined that individuals having low-risk prostate cancer that undergo active surveillance could gain from vitamin D3 supplementing. It has been shown in current meta analyses that raised danger of ischaemic heart disease, myocardial infarction as well as premature mortality correlates well with low levels of plasma 25(OH)D [126]. Despite the fact that three individual intervention RCTs revealed negative results regarding usage of vitamin D3 as a beneficial therapeutic agent in cancer [117, 122, 127] it was suggested to be contributor in reducing the levels of cancer mortality [128]. Although the RCT evidence cannot allow identifying a marked serum level 25(OH)D, it provides a platform to sustain a crucial function of vitamin D within cancer mortality [68].

The Effect of Vitamin D on Cardiovascular Disease

Cardiovascular (CV) risk factors, such as arterial hypertension, obesity, diabetes mellitus, as well as CV disorders, including myocardial infarction, coronary artery disease or stroke, account for the major causes of death at the global levels, particularly in western developed countries [129]. This highlights the importance of further understanding the function of vitamin D within the context of CVD. The contractile features of cardiomyocytes are mostly regulated by the immediate contact amid the contractile proteins, actin and myosin, calcium as well as the intracellular calcium levels. The extracellular calcium homeostasis regulated through extents of vitamin D influence the intracellular calcium levels and may impact contractility of cardiac cells [130]. Calcitriol, the dynamic form of vitamin D (1,25-dihydroxyvitamin D) virtually regulates several critical cellular and biological processes of virtually all body cells, including cardiac cells, epithelial cells, endothelial cells as well as vascular smooth muscle cells via the regulation of the cytosolic vitamin D receptor (VDR). Despite the fact that this control varies according to cell type, it is essential in cardiac cells as they are mainly reliant on the blood intensity of calcitriol [131, 132]. Concomitantly, the ablation of VDR receptors has numerous profound negative influences on cardiac cells. For instance, separated cardiac cells from VDR knockout mice are characterized by having raised contraction and relaxation rates which are independent of extents of calcitriol with respect for levels of control mice [133, 134]. Of note, cellular hypertrophy causing cardiomegaly was observed in VDR knockout mice tissues [135]. This has been attributed, at least in part, to the reality that tissue inhibitors of matrix metalloproteinases were remarkably mitigated in VDR knockout mice with respect to control mice [135]. The abrogation of the inhibition of matrix metalloproteinases results in progressive left ventricular remodelling

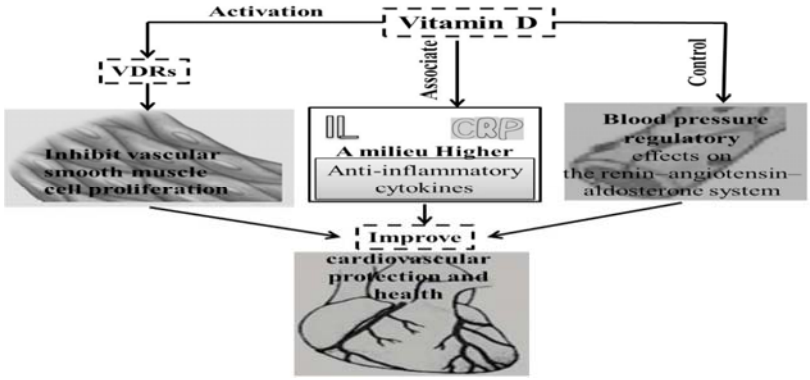

Fig. (5). Mechanism of action of vitamin D in cardiovascular disorders.

and heart failure [136]. Calcitriol mediates a central role, though modulating the activity of VDR, the morphology, and proliferation of cardiac cells. It was revealed that calcitriol mediates the up-regulation of the levels of the cardiac muscle protein, myotrophin, mitigates the articulation of atrial natriuretic peptide, and upregulates and induces nuclear localisation of the VDR [134, 137]. Concomitantly vitamin D3 deficiency in rats was shown to be in positive correlation to hypocalcaemia, augmentation of plasma parathyroid hormone, mitigation in myofibrils magnitude, and buildup of collagen fibres, causing interstitial fibrosis [138]. Nonetheless, calcitriol augmentation has been shown to mediate the prevention of cardiac hypertrophy. For example, upon calcitriol treatment in rats with impulsively hypertensive heart failure, a decrease in heart weight was observed along with a decrease in myocardial collagen levels, left ventricular diameters with respect to untreated rats [134]. VDR receptors have been shown to exhibit different genotypes. Of note, a recent investigation examined the correlation amid VDR gene alternatives and ischemic stroke within an Indian populace. Three sole nucleotide polymorphisms of the VDR gene were examined and genotyped employing PCR-RFLP technique, and evaluated for correlation (Fok I, Apa I, and Taq I), both Apa I and Taq I polymorphisms were not shown to be correlated with ischemic stroke. Nevertheless, the genotype of Fok I was observed to render 2.97-fold danger of ischemic stroke (95% CI = 1.16–7.63, p = 0.02) with respect for FF genotype of Fok I. This correlation was shown to be autonomous of different demographic as well as pivotal biochemical features encompassing age, smoking, sex and alcohol consumption, serum glucose, insulin, 25 hydroxyvitamin D, lipid profile as well as extents of plasma nitric oxide [OR = 2.27, 95% CI = 1.25– 4.09, p = 0.01] [139].

Potential Mechanisms of Action for a Link Amid Vitamin D and Coronary Heart Disease

Vitamin D receptors (VDRs) exist in diverse kinds of cells and tissues encompassing vascular smooth muscle cells [140], cardiomyocytes, and coronary arteries [141, 142]. Due to the abundance of VDRs in the vascular system, as well as the coronary arteries, it was suggested that there could be a mechanistic route through which vitamin D mediate cellular actions that may improve cardiovascular health. For instance, VDRs activation has been illustrated to inhibit vascular smooth muscle cell propagation, which is thought to act as cardioprotective [143]. Of note, previous lines of evidences have linked the greater 25OHD levels and/or vitamin D augmentation to a systemic anti- inflammatory condition through the impact on interleukins, C- reactive protein, and anti-inflammatory cytokines— molecular cascades that are thought to foster cardioprotection [144-146]. Interestingly, it was shown that vitamin D regulates blood pressure via its controlling actions on the renin–angiotensin– aldosterone structure [147]. Few studies have proposed that vitamin D augmentation might attenuate the occurrence of abrogated glucose acceptance and diabetes mellitus [148, 149], in addition to enhancing standards for lipid parameters [150]. Additionally, the findings from various researches have proposed a connection amid vitamin D and a reduced possibility of autoimmune circumstances like rheumatoid arthritis [151], diabetes (both type 1 and type 2) [152, 153], as well as multiple sclerosis [154] (Fig. **5**).

Clinical Trails

In several previous tests, calcitriol augmentation has been illustrated to decrease blood pressure, angiotensin II amounts, plasma renin operation, as well as myocardial hypertrophy [155, 156]. It was highlighted that normal contact with ultraviolet B radiation augmented distribution of 25(OH) D with level 100 nmol/l and considerably attenuated blood pressure by an estimated 6 mmHg for hypertensive individuals with primary 25(OH) D amounts of 26 nmol/l in an intervention time frame of six weeks [157]. Of note, a further research revealed that elderly women lacking in vitamin D who were treated with calcium and 20 lg vitamin D3 each day had augmented levels in serum 25(OH) D of 20 nmol/l ($p < 0.01$), a mitigated levels of serum parathyroid hormone of 17% ($p < 0.05$), and attenuated levels of systolic blood pressure of 9.3% ($p < 0.025$), and a reduction in heart rate of 5.4% ($p < 0.025$) with respect to the patients who were only supplemented with calcium [158]. Thus, a regular amount of circulating calcitriol is pivotal for calcium homeostasis and for the homeostasis of electrolytes, capacity, as well as blood. Previous work disclosed the availability of a correlation between vitamin D lack with the well-documented atherosclerosis susceptibility factors (Fig. **6**), including obesity, glucose intolerance, HTN, and hyperlipidemia [9, 159, 160]. A previous study that included, a cross-sectional characteristic specimen of the U.S. populace, revealed a considerable rise in the incidence of HTN [OR = 1.30 (1.13–1.49); $p < 0.001$], diabetes mellitus [OR = 1.73 (1.38–2.16); $p < 0.001$], obesity [OR = 2.29 (1.99–2.63); $p < 0.001$], and increase in triglyceride levels [OR = 1.47 (1.30–1.65); $p < 0.001$] in individuals having vitamin D levels of below 21 ng/mL with respect to those having relatively greater levels than 37 ng/mL ($p < 0.001$) [160]. That correlation was significantly improved by a newer research which connected vitamin D shortage with an augmented danger of hyperlipidemia (HR = 1.12, p = 0.002), diabetes (HR = 1.33, $p < 0.0001$), and HTN (HR = 1.26, $p < 0.0001$) in vitamin D deficient people [9].

The pivotal function of vitamin D within the etiology and pathology of CAD is connected to atherosclerosis and could concern vascular calcification as well. Due to decreased renal calcitriol synthesis, in conjunction with alternative elements, secondary hyperparathyroidism is caused within the initial phases of chronic kidney disease [161]. For individuals with end-stage renal disease, secondary hyperparathyroidism may be contemplated as an essential risk element in the pathology processes of CAD that results in vascular calcification [162]. It was demonstrated that in hemodialysis individuals, the administration of active vitamin D and/ or synthetic

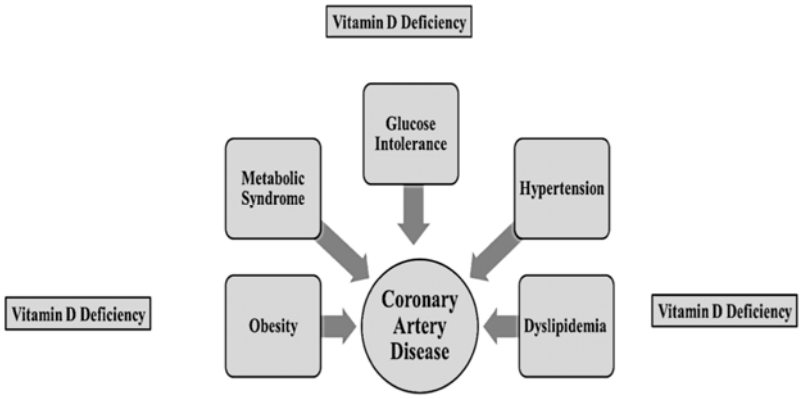

Fig. (6). The association linking vitamin D and CAD risk elements.

vitamin D analogs mitigated the danger of mortality from cardiovascular disorder [163]. Speaking generally, it was hypothesized that the availability of vascular calcification is a forecaster of inferior five-year rates of survival [164]. Remarkably, the usage of calcitriol was demonstrated to be inversely associated with the rate of vascular calcification, irrespective of alternative elements related to ischemic heart disorder [165]. In a nonrandomized prospective study where the members had no previous cardiovascular disease, patients with reduced 25(OH) D levels and defined as: <37.5 nmol/l had a relatively augmented rate of myocardial infarction disorder, coronary inadequacy, and heart failure [adjusted hazard ratio (HR) = 1.62; (1.11–2.36); p = 0.01] with respect to those having regular extents. Nonetheless, this impact was observed within hypertensive subjects [HR = 2.13; (1.30– 3.48)] as opposed to the normotensive ones [HR = 1.04, (0.55–1.96)] [166]. On the other hand, gender was shown to have a function on the influence that vitamin D lack has towards CAD. Although men with reduced 25(OH) D extents (637 .5 nmol/l) showed a greater susceptibility to [comparative risk RR = 2.09 (1.24–3.54)] of myocardial infarction with respect to men with adequate extents (675 nmol/l) following adjustment for diverse standards of living and alternative risk elements, this feature was dissimilar for women [167]. However, a newer research revealed that extents of vitamin D could be autonomously associated with the danger of cardiovascular disorders. In a unit comprising 14,641 males and females where their age range was 42–82, in the time frame from 1997 to 2000, and who were observed until 2012, augmented levels of 20-nmol/L 25(OH) D were related to HR of 0.92 ([0.88–0.96]; p < 0.001) for complete mortality and 0.96 ([0.93–0.99]; p = 0.014) for frequency rate of cardiovascular disease, in both men and women [168]. The extent of vitamin D has been associated with several clinical and laboratory parameters of CHF, encompassing, NT pro-BNP(N-terminal domain of the prohormone brain natriuretic peptide), NT-proANP (N-terminal of the prohormone atrial natriuretic peptide) as well as LVEF (left ventricle ejection fraction) (Fig. **7**). Another study revealed that following multivariable adjustments for several crucial elements, the inverse association of NTpro-BNP with 25(OH) D and calcitriol extents was still evidenced (b coefficient= - 0.082; p < 0.001) and (b coefficient= - 0.180; p < 0.001) respectively [169, 170]. Likewise, in CHF patients, the extents of 25(OH) D and calcitriol have an inverse correlation with NT-proANP (r = 0.16; 2 p < 0.001 and r2 = 0.12; p < 0.01, correspondingly) [171].

Additionally, intensity of vitamin D was shown to be correlated to functioning of the left ventricle. 25(OH) D and calcitriol extents were inversely associated with abrogated left ventricle operation (p < 0.001 for both), and this correlation remained noteworthy following multivariable adjustments (p < 0.001 for both) [169, 37]. Likewise, raised NYHA categories were additionally correlated to reduced extents of 25(OH) D and calcitriol (p < 0.001 for both) [169].

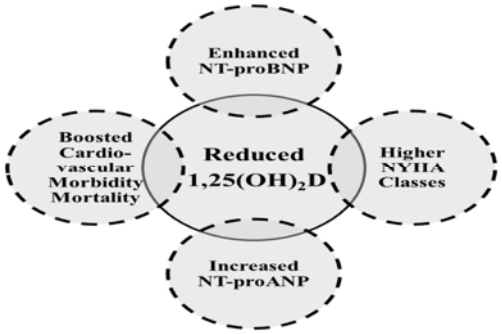

Fig. (7). The association linking vitamin D extents and the clinical and laboratory parameters of congestive heart failure.

Alternatively, a current research which observed 3731 men of ages ranging between 60–79 years with no prior heart failure and observed them over a mean period of 13 years revealed that the danger of developing heart failure was associated to Parathyroid Hormone (PTH) extent as opposed to those of 25(OH) D. Increased PTH (P55.6 pg/mL) has been shown to significantly correlate with an augmented rate of incident HF following consideration of daily life features and comorbidities (HR = 1.66; [1.30–2.13]). Of note, the association linking 25(OH) D extents and incident HF was not important [172]. Lack of vitamin D has been shown to be related to augmented danger of chronic cerebral small vessel disease [173]. A contemporary research on 59 successive individuals who had acute ischemic stroke or transient ischemic attack illustrated that 25(OH) D extents under 25 nmol/L were related to lacunes (regression coefficient, 0.5; 95% CI, 0.04–0.95), severe white matter (OR = 2.74; [1.31– 6.45]), and profound cerebral micro- bleeds (OR = 1.68; [1.03–2.78]) [173]. Vitamin D deficiency was found to be associated with increased danger of mortality and cardiovascular mortality in numerous researches. Continuation of the 3258 members in another research covering a median time frame of 7.7 years revealed that individuals who had acute and mild deficiency in extents of vitamin D (median concentrations of 25(OH) D of 19.0 and 33.3 nmol/l) had greater occurrence of mortality [HR = 2.08, (1.59 –2.70) and HR = 1.53 (1.17– 2.01), correspondingly, and cardiovascular mortality [HR = 2.22; (1.57–3.13) and HR = 1.82 (1.29–2.58),accordingly, with respect to individuals with regular extents (median levels of 71.0 nmol/l). Other recent comparable studies were observed for individuals bearing the minimal calcitriol levels [170, 174]. Another research covered 946 members with some cardiovascular disorder in California over a median of eight years and lately demonstrated that concentration of below 20 ng/mL were autonomously correlated to cardiovascular occurrences (HR = 1.30 [1.01–1.67]) even following normalisation for some elements such as season of blood quantification and health behaviours [175].

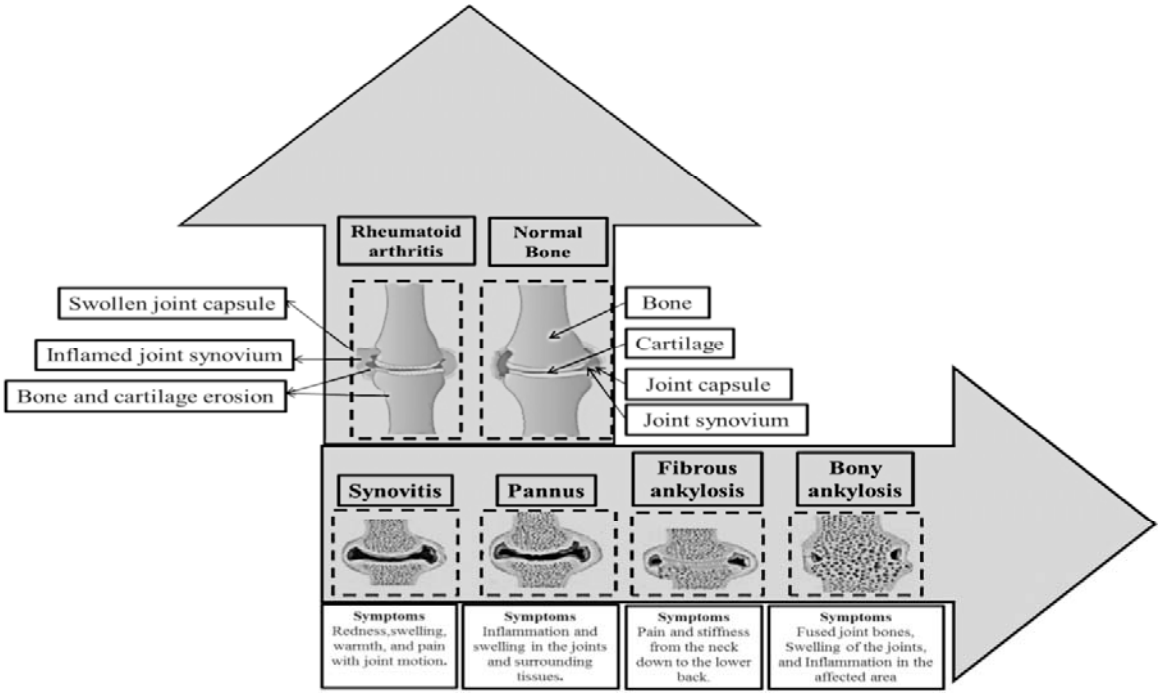

Fig. (8). Rheumatoid arthritis (RA) progresses with healthy and diseased Bone.

Vitamin D in Rheumatoid Arthritis

Rheumatoid arthritis (RA) (Fig. **8**) comprises an advanced inflammatory disease characterised by inflammation of the synovium which results in degradation of joint bone and cartilage. Genetic elements are renowned to add to molecular and cellular events underpinnings the pathology of RA.[176]. Furthermore, broad spectrums of ecological elements which encompass smoking and alcohol consumption [177, 178] as well as several dietary factors have additionally been illustrated to add to the danger of RA [179-181]. Prompt diagnosis and adequate therapy strategies are essential in mitigating the affliction of this disorder, however the pathogenesis of RA is currently elusive [182]. Vitamin D may be one of the ecological elements pertinent with RA [183]. Of note, there is a greater relevance of osteoporosis within RA individuals [184]. Recent evidence demonstrates that vitamin D could be correlated inversely with the incidence, advancement, and disease operation of RA [185-187]. The anti-inflammatory and immunomodulatory functions of vitamin D have recently become obvious [188].

Cellular Targets for Vitamin D in RA

The result that particular receptors for 1,25(OH) 2D were articulated by lymphocytes from individuals with RA was the initial line of proof that provides linkage between vitamin D and immune operation [189]. VDR articulation was observed in numerous alternative immune system cells [35], supporting a broad range of possible activities for 1,25(OH) 2D. These involve intrinsic antibacterial reactions in monocytes and neutrophils, modulate the antigen provision by DCs, and regulation of T-cell and B-cell phenotype and operation [190, 191]. Of note, immune-cell and stromal-cell communications are implicated within RA pathology, along with pivotal inflammatory links aggregating in joint damage as the equilibrium amid bone-reducing osteoclast and bone-generating osteoblast operations changes in view of bone damage. T cells, macrophages and fibroblast-like synoviocytes (FLSs) are key cellular mediators in RA, yet B cells and DCs mediate a crucial role [192]. To assess the possible pertinence of vitamin D within the pathology of RA, it is thus crucial to contemplate the functions of these diverse cell kinds within RA pathogenesis as well as the influence of vitamin D on all of them. In RA, it was reported that lack of vitamin D mediates inflammatory reactions as well as osteoclast-controlled bone loss. Of note, 25(OH)D is metabolised to 1,25(OH) 2D by 1α- hydroxylase-articulating APCs, to support the distinguishing of TolDCs, that mediate the distinguishing of TREG cells and BREG cells. 1,25(OH) 2D generated by APCs or BREG cells could additionally act immediately on T cells and B cells in order to support an anti-inflammatory phenotype, and augment articulation of OPG above RANKL by FLSs, thus decreasing osteoclastogenesis, diverse cell variation pathways, cytokine generation and function and vitamin D metabolism.

Clinical Studies

It has been revealed that rheumatoid arthritis patients have reduced levels of vitamin D serum values as opposed to healthy controls, and that amid individuals with RA there is inverse correlation linking vitamin D serum values and RA disease progression rate. This meta-analysis followed previous reports that suggested a considerable inverse link amid serum 25OHD intensities and disease activity score in 28 joints (DAS28) in individuals with active RA (DAS28 $\geq$ 2.6) [193, 194]. Another report [195] was unable to disclose a numerically significant relationship linking 25OHD and DAS28 after the adjustments of mutli-variables within individuals with rheumatoid arthritis. On the other hand, Cutolo, Otsa [196] found a strikingly inverse association linking 25OHD and DAS28 levels in southern European individuals and in northern European individuals, yet with no considerable differences with regard for 25OHD values amid Estonian and Italian RA individuals and their controls. Of note, another previous pilot study [197] revealed that 25OHD extents were significantly reduced in patients who reacted unsuccessfully to therapy. A systematic review made available in 2010 [198] catalogued 7 researches appraising vitamin D insufficiency level within RA patients with respect to fit controls. Few of such researches reported reduced concentrations of vitamin D in RA, while the other five did not. Despite the fact that the quantitative synthesis findings did not establish a considerable numerical variation regarding the frequency of shortage of vitamin D (25OHD<50nmol/L) within RA patients and fit negative controls, one could note that 25OHD extents in RA patients are unfailingly

reduced compared to those in healthy control subjects. It was revealed that reduced extents of vitamin D have a correlation with greater incidence of RA, as was reported in a previous report by Song, Bae [199]. It is additionally noteworthy that serum 25OHD levels were not associated with disease operation in RA patients, who were complemented with physical dispensation of vitamin D during a short time frame [187, 200, 201]. A randomised controlled test carried out by Gopinath, *et al* [202] suggested the pain relief operation of 1,25(OH) 2D in disease modifying anti Rheumatic drugs (DMARD)-naive RA [202].

Impact of Vitamin D on Ovarian Reserve Markers

Polycystic ovary syndrome (PCOS) and *in vitro* fertilization (IVF) VDR exist in diverse kinds of tissues and cells like the immune system (T and B cells, macrophages and monocytes), the endocrine structure (pancreas, pituitary, adrenal cortex and thyroid), as well as the reproductive structure (ovaries, uterus, placenta and endometrium) [2]. VDR is present in the nuclei and cytoplasm of granulosa cells (GC) of human ovaries which is suggestive that it mediates the physical roles of 1,25(OH) 2D3 in ovarian follicles [203]. Recently it has been stated that VDR mRNA is articulated in the combined ovarian cell and in a cleansed GC culture [204]. The selective availability of VDR in female reproductive tissues is an indication that vitamin D may be concerned in female reproduction procedures. Current evidence suggests the presence of a relationship linking vitamin D and ovarian reserve markers. Notably, there is data regarding the manner in which vitamin D influences ovarian reserve markers, especially anti-Müllerian hormone (AMH) [205-209]. Of note, AMH, or Müllerian inhibiting substance (MIS), comprises a gonadal-particular glycoprotein which is part of the transforming development element superfamily. Upon male fetal sex separation, AMH is selectively discharged by sertoli cells and subsequently causes the deterioration of the Müllerian ducts [210]. In females, AMH is generated by GC of developing small follicles, of particular interest is the prenatal follicles, yet this is not secreted prior to the birth period [211]. Small alterations within AMH concentration within the menstrual cycle as well as its particular synthesis by developing ovarian follicles provide a pivotal biomarker for a technique designated as assisted reproductive technology (ART) [211]. Despite the fact that AMH comprises one of the most suitable diagnostic indicators for ovarian reserve, previous works have revealed that contextual elements like vitamin D insufficiency may change its articulation and serum extents [205-208, 212]. PCOS comprises one of the most widespread endocrine diseases in females of reproductive age, which affects as many as 18% of this populace. PCOS is featured by ovulatory abrogation resulting in anovulation; biomedical/biochemical or features of hyperandrogenism; and polycystic ovary morphology [213]. The diverse clinical modulations of the disorder involve obesity, insulin resistance (IR) and ovulatory infertility [214]. *In vitro* fertilisation (IVF) comprises one of the methods of assisted reproduction created to enhance possibilities of attaining pregnancy. Within the regular IVF technique with managed ovarian hyperstimulation (COH), progress and growth of several follicles are induced via employment of gonadotrophins, usually integrated with a gonadotrophin-discharging hormone (GnRH) agonist or antagonist [215]. It has been reported that lack of vitamin D has appeared as an element that affects female infertility and IVF result parameters. Of note, positive findings establish the relationship between serum or follicular fluid concentrations of vitamin D and the outcomes of IVF, particularly regarding clinical pregnancy rates (CRP) [216-221].

Clinical Studies

It has been highlighted that the level of seasonal differentiation in a woman's AMH levels have correlation with the level of 25(OH)D extents variations. It was stated that vitamin D additions could avert seasonal differences in vitamin D as well as AMH extents [208]. Successively, another investigation appraised the impact of 1,25(OH) 2D3 supplementation on extents of AMH serum in a number of female subjects lacking vitamin D with no polycystic ovary syndrome (PCOS). Despite the fact that the individuals were given oral vitamin D additions, there was no considerable alteration in amounts of AMH serum (p=0.6) [222]. Previous work regarding vitamin D condition in PCOS patients revealed that lack of vitamin D was widespread amid females with PCOS with respect to fit women [223- 225]. This lack may be concerned with a number of elements of PCOS such as obesity, ovulatory abrogation, and metabolic disorder [226, 227]. Alternatively, Mahmoudi *et al*. [228] contrasted extents of serum vitamin D in a number of PCOS females with respect to other control females. They observed greater serum extents of vitamin D within PCOS females (29. 3 ng /ml) with respect to controls (19. 4 ng /ml) [228]. Ozkan *et al*. [215] have noted that females who attained clinical pregnancy had remarkable augmented 25(OH)D amounts within their serum and follicular fluid with respect to non-pregnant subjects. Any ng/ml enhancement in follicular fluid 25(OH)D augmented the possibility of attaining clinical pregnancy with an increase of about 6%. Similarly, the implantation incidence was remarkably augmented in individuals who had raised 25(OH)D extents [215]. Alternative researches, nonetheless, did not agree with these results [217-219]. Anifandis *et al* [216] observed that greater amounts of 25(OH)D in follicular fluid influenced, in a negative manner, the quality of embryo and resulted in inferior IVF results. During this investigation, females with adequate extents of 25(OH)D within follicular fluid (>30 ng /ml) generated low -standard embryos and comprised a reduced possibility of attaining clinical pregnancy with respect to females with inadequate (20.1- 30 ng /ml) or insufficient (<20 ng /ml) 25(OH)D extents [216]. In contrast, the results from another study sustained no association linking vitamin D amounts within serum and follicular fluid with IVF result [218]. Another pilot research on 173 females subsequent to IVF suggested that women who had adequate concentrations of serum 25(OH)D (≥30 ng /mL) had augmented the possibility of attaining clinical pregnancies subsequent to IVF [219]. Nonetheless, there were no significant variations noted amid females with adequate and inadequate 25(OH)D extents within the IVF sequence factors which involved dose of gonadotropin and endometrial thickness [220]. Remarkably, Rudick *et al*. [221] have revealed that there could be an association linking vitamin D and IVF achievement and this may be influenced by the patient's ethnicity [221].

IMMUNE FUNCTION

The mammlian immune system is composed of two unique yet interacting kinds of immunity: adaptive and innate. The innate immune machinery comprises the stimulation of Toll-like receptors (TLRs) within polymorphonuclear cells (PMNs), and macrophages and within several epithelial cells. TLRs are a large family of transmembrane pathogen-identification receptor proteins which selectively communicate with selective membrane sequences (pathogen-associated molecular pattern [PAMP]) secreted by transmittable agents which elicit the instinctive immune reaction within the host. TLRs stimulation may result in the induction of antimicrobial peptides (AMPs) such as cathelicidin and reactive oxygen species (ROS) that can mediate the killing activity against the infecting organism. Of note, the induction of increasing levels of cathelicidin is mediated via 1,25(OH)2D in myeloid as well as epithelial cells [229]. Lipopeptide-derived from *M. tuberculosis* activates TLR2 in macrophages [230] and subsequently leads to augmented levels of expression of CYP27B1 and VDR, upon availability of target substrate (25OHD), mediates the induction of cathelicidin. Therefore, the proper levels of vitamin D can support the instinctive immune reaction. On the other hand, the adaptive immune reaction is commenced by antigen presenting specialised cells, dendritic cells and macrophages and subsequently activating cells answerable for antigen identification, the T and B lymphocytes. Most notably, the kind of T cell activated and its type inside

the helper T cell class Th1, Th2, Th17 and Treg are reliant on the cellular setting in which the antigen is provided in what kind of cell and in which cellular micro environment. Of note, vitamin D was illustrated to exert an inhibitory function on the adaptive immune structure. It was shown that 1,25(OH)2D attenuates the maturation of dendritic cells, and thus dampening their capability to provide antigen and subsequently to stimulate T cells [231]. Moreover, it was shown that 1,25(OH) 2D mitigates the maturation of Th1 cells able to yield IFN- g and IL-2, and Th17 cells generating IL-17 [232]. The underlying mechanism involves the attenuation of IL-12 generation, Th1 advancement, IL-23 and IL-6 generation and Th17 maturation and operation. Nonetheless, from the clinical perspective, there are no current verified vitamin D drugs for immunotherapeutic purposes. However, the correlation between tuberculosis and vitamin D deficiency is well documented [233]. Previous animal model investigations have revealed the function of 1,25(OH) 2D as well as its analogs in the treatment of autoimmune disorders [234] and as adjuncts to immunosuppressants following transplantation procedures [234] which are also compelling, but as for the treatment of infections, clinical trial data are still to be investigated.

CONCLUSION

Vitamin D has been of central notice due to the remarkable growth in the amount of scientific research publications implying that vitamin D could comprise a key function in the delaying of carcinogenesis, in addition to a multitude of non-skeletal and skeletal diseases. Mounting facts suggest that lack of vitamin D is correlated with an augmented danger of death and cancer development in addition to alternative chronic disorders. Previous bodies of work in cells and animal models significantly support an anti-neoplastic function of vitamin D. Nonetheless, there are some inconsistencies in the epidemiological reports, as there are some reports which indicate positive and others indicate negative results. Despite the fact that some previous works reveal the enhanced cancer development danger upon lack of vitamin D, several other reports employing pre-diagnostic 25(OH)D extents do not sustain this conjecture, apart from the case of colorectal cancer. Since an estimated 150,000 colorectal cancer instances within the US and 1,000,000 incidences globally are diagnosed every year and given the anticancer influence of vitamin D were correlated tightly with colorectal cancer, this may solidify the notion of awareness that lack of vitamin D must be averted for cancer prevention purposes. Several preclinical findings highlight the mechanism of calcitriol-mediated regulation of crucial molecular pathways and how this might attenuate the development and progression of multiple kinds of cancers. The development and studying of vitamin D metabolites or analogues can provide a helpful platform to target some kinds of cancer, particularly when used in combination with existing therapies. Unhealthy and poor lifestyles contribute to susceptible elements for cardiovascular disorders or obstacles and are additionally associated with lack of vitamin D. Mounting lines of evidences strongly suggest that vitamin D insufficiency is associated with a wide spectrum of cardiovascular pathologies as well as their risk elements. Moreover, it has been shown to be correlated to the increased rate of mortality. Concomitantly, vitamin D supplementation may provide a possible avenue in treating some of these pathologies and hence contribute to the decrease in morbidity and mortality rate resulting from cardiovascular disease. However, all these data suggest that, at least in the major part, correlations do not necessarily reveal the causation. Of note, vitamin D levels may act as a lifestyle biomarker. It remains to be addressed if vitamin D enhancement could affect the progression and/or occurrence of cardiovascular disorders in vitamin-D-deficient individuals. Earlier researches on vitamin D established that the augmented aptitude for generation of dynamic 1,25(OH) 2D by mammalian immune cells within the joint, and links this generation to immune operation and on the possible progression of hypercalcaemia. Nonetheless, current reports have revealed a connection linking vitamin D state (as detailed by serum intensities of 25(OH)D) and RA danger and advancement, resulting in a boost in the amount of serum 25(OH)D assays done in individuals who have this disease. Although there are several reports indicating a function for reduced serum 25(OH)D in RA advancement, the concrete confirmation is still elusive, and is challenged by the increasing complexity and numerous elements involved. Of note, the variations in the operation of renal and extra-renal vitamin D metabolism that are linked to RA significantly suggest that the implications of vitamin D addition or 1,25(OH) 2D treatment tend to differ dependending on the stage or phase of the disease. Taken together, we propose that future investigations that may work on (I) RCTs may intend to decrease, avert or address early disease rather than implementing these regimens only in patients with very advanced stages of cancer where multiple potent therapeutic drugs have failed; (II) imminent RCTs are necessary to elucidate the most favourable target amounts of serum 25(OH)D and when is the precise timing for supplements or drugs to be introduced; (III) establishing which serum 25(OH) D3 extents may act as a biomarker of health-associated results; (IV). Further studies on cardiovascular disease within vitamin-D-inadequate or vitamin-D- lacking patients may be warranted in RCTs; and (V) In due course, randomized controlled tests on vitamin D addition in patients who have active disease are needed to look at the influence of vitamin D on the commencement and progression of RA. Future research apparently requires extension in later research on vitamin D within the RA context.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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