Review

Effect of Vitamin D Supplementation in Prostate Cancer: A Systematic Review of Randomized Control Trials

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Received: September 4, 2017; Accepted: August 7, 2018

Abstract: Vitamin D is important in many cellular functions including cell cycling and proliferation, differentiation, and apoptosis. Via the induction of cell cycle arrest and/or apoptosis, vitamin D inhibits normal prostatic epithelial cells growth. Review the evidence of the effect of vitamin D supplementation on prostate cancer (PC) biomarkers and patient survival and assess optimal dosage, formulation and duration. Pubmed, Medline and Ebsco Host databases were systematically searched for relevant literature. 8 Randomized Controlled Trials were included in this review. All studies, besides one, were of high methodological quality. 4 studies used calcitriol (0,5-45 μg/weekly), 2 studies have used vitamin D3 (150-1000 μg/daily) and 2 other studies have used 1α-hydroxy Vitamin D2 (10 μg/ daily or weekly). Duration of supplementation varied between 28 days up to 18.3 months. Two studies had positive effects on prostate specific antigen (PSA) ($p < .05$), 1 study had a significant positive effect on median survival ($p < .05$) and 1 study showed a significant reduction of vitamin D receptor (VDR) expression ($p < .05$). The remaining studies showed negative or no effect on PC characteristics, clinical outcomes and/or survival. Current evidence suggests that vitamin D supplementation in conjunction with standard of care (e.g. chemotherapy, radiation therapy) may confer clinical benefits such as a decrease in serum PSA levels and VDR expression but further research is required to ascertain these results. Calcitriol supplementation in doses ranging from 250-1000 mg for 3–8 weeks or a lower dose of 45 mg for 18.3 months, appear most beneficial regarding outcomes of PC progression and survival.

Keywords: Vitamin D, Calcitriol, PC, VDR, PSA, randomized controlled trial

Introduction

Vitamin D, also called calciferol, refers to a group of fat-soluble pro-hormones, which exist in two forms, vitamin D2 or ergocalciferol, and vitamin D3 or cholecalciferol. Cholecalciferol can be synthesized endogenously in the skin under the influence of solar ultraviolet radiation [1], while it is also found in animal foods. Ergocalciferol derives mainly from plant foods and dietary supplements [2]. However, both forms of calciferol are converted to 25-hydroxyvitaminD, 25 (OH) D or calcidiol, the inactive storage form of the vitamin, in the liver, and thereafter, calcidiol is converted to the active form of the vitamin, i.e. 1,25-dihydroxyvitamin D or calcitriol, in the kidneys [3]. Based on the recommended dietary allowance (RDA) published by the Food and Nutrition Board (FNB) at the Institute of Medicine of The National Academies (formerly National Academy of Sciences) for people between 1–70 years, is not higher than 600 IU/day, while for the elderly (>70 years) it is 800 IU/day [4].

Based on the initial observations of prostate cancer mortality rates in the United States, which were inversely related to ultraviolet light exposure, vitamin D deficiency has been ascertained to increase the risk of Prostate Cancer (PC). Therefore, in addition to its well-established role in the regulation of calcium homeostasis in the body, vitamin D has been shown to exhibit antitumorigenic properties [5] Although the molecular pathways of this process are not known, studies investigating the anti-proliferative properties of vitamin D on the prostate, showed that through the induction of cell cycle arrest and/or apoptosis, it inhibits the growth of normal prostatic epithelial cells, as well

as primary cultures of PC cells and cell lines [5–7] Furthermore, the vitamin D receptor (VDR), a nuclear receptor for which calcitriol is the main biologically active ligand has gained considerable attention in an effort to decipher the role of vitamin D in oncology. Indeed, the importance of VDR for the treatment of cancer has been shown in many studies. [8–10]. Expression of VDR is seen in a wide range of tumors and the anti-proliferative activity of VDR ligands has been demonstrated in many common human malignancies, including PC [11].

According to the World Health Organization (WHO), PC is the 2nd cause of cancer-related death in men after lung cancer. In 2012, 1.1 million cases were diagnosed with PC worldwide, representing 15% of all cancers diagnosed in men [12]. As a result, the high incidence of the disease indicates a great necessity for new clinical protocols intended for early diagnosis (screening) and treatment.

Prostate specific antigen (PSA) is currently the most commonly used marker for the diagnosis of prostate tumors, despite several disadvantages of its use [13]. However, total PSA measurement includes both bound PSA and inactive free PSA. Free PSA is the biomarker associated with a benign prostate disease; thus, a higher free/total ratio of PSA has been proposed as an adjunct measure to reduce unnecessary biopsies and increase accuracy of PC prognosis. [14] Furthermore, free PSA is made up of several PSA subtypes, including pro-PSA. Higher levels of pro-PSA, called [–2]pPSA are found in men with PC, [15] and therefore, prospective studies have suggested that pro-PSA may be used to distinguish between PC and benign prostatic disease.[16] A further derived measure is the prostate health index (PHI), which uses a formula to combine the total and free PSA and pro-PSA. The PHI has been reported to improve the prediction of PC [17]. None of the above adjunct markers – besides PSA – are being used in standard clinical practice for the detection and progression of PC. Although based on current recommendations, PSA is considered insufficient to serve as a sole screening tool, it remains useful for follow up and early detection of disease recurrence in clinical practice.

Previous studies have shown inconsistent results regarding vitamin D supplementation and PC clinical biomarkers such as PSA levels. For instance, significant decreases in plasma PSA levels after calcitriol supplementation in patients with PC [8,18] have been described indicating a potential therapeutic effect. In contrast, other studies have shown that daily oral administration of calcitriol in patients with PC has no significant effects on PSA levels [19].

Many observational studies have shown a negative correlation between vitamin D levels and PC progression after treatment [20], whereas results of experimental and clinical studies are even more conflicting [21]. Moreover, the literature has yet to provide specific evidence for the potentially beneficial effect the long-term vitamin D treatment of patients with PC, since the majority of current studies are short-term` (up to 36 weeks) [22]. Furthermore, most of the studies in patients with PC do not investigate the effects of vitamin D as a monotherapy, since it is often combined with other established cancer therapies [23].

The main purpose of this systematic review was to investigate the effect of vitamin D supplementation on specific clinical and epidemiological outcomes of PC, such as PSA levels following treatment, the expression of VDRs and the overall survival of the patient, as evidenced in randomized control studies (RCTs). Specific objectives included determining dosage, formulation and duration of vitamin D supplementation required for positive clinical outcomes and effective monotherapy or combination treatment of PC.

Methods

Literature search

Pubmed, Medline and Ebsco Host databases were systematically searched for relevant literature. All available literature published up to January 2017 was examined including all studies published in English language. The specific keywords used regarding exposure and outcomes were: [1,25-dihydroxycholecalciferol OR vitamin D OR ergocalciferol OR calcitriol OR BXL628 OR vitamin D2 OR cholecalciferol OR DN-101 O R 1α-Hydroxyvitamin D2 OR 1a-Hydroxyvitamin D2] AND [PC OR PC treatment OR prostatic hyperplasia OR vitamin D receptor OR VDR OR overall survival OR survive OR mortality OR vitamin D metabolites OR prostate Specific Antigen OR PSA] AND [randomized controlled trial OR randomized OR RCT]. When searching in international databases Title/Abstract και Abstract were used as filters. A complete manual search of the reference lists from original studies was conducted. Search results are shown in Table 1.

Study selection

All studies selected were RCTs that evaluated the effect of Vitamin D supplementation on PC outcomes such as PSA levels, VDR expression, and patient survival. Study populations included men, regardless of age, race and ethnicity diagnosed with PC.

The exposure was determined as oral vitamin D supplementation (μg or IU). The supplements included were eit-

Table 1. Search results per keyword and keyword combination

Keywords		EBSCO	PubMed
((((((Prostate cancer[Title/Abstract]) OR Prostate cancer treatment[Title/Abstract]) OR prostatic hyperplasia[Title/Abstract]))	#1	268 001	94 561
(((Randomized controlled trial[Title/Abstract]) OR Randomized[Title/Abstract]) OR Rct[Title/Abstract])) ((((((((((Vitamin D receptor[Title/Abstract])	#2	1 154 490	385 474
OR VDR[Title/Abstract]) OR Overall survival[Title/Abstract]) OR Survive[Title/Abstract]) OR Mortality[Title/Abstract]) OR survival[Title/Abstract]) OR vitamin D metabolites[Title/Abstract]) OR Prostate Specific Antigen[Title/Abstract]) OR PSA[Title/Abstract]))	#3	3 657 078	1 228 608
((((((((((1,25-dihydroxycholecalciferol[Title/Abstract]) OR vitamin D[Title/Abstract]) OR ergocalciferol[Title/Abstract]) OR calcitriol[Title/Abstract]) OR BXL628[Title/Abstract]) OR vitamin D2[Title/Abstract]) OR cholecalciferol[Title/Abstract]) OR DN- 101[Title/Abstract]) OR 1α-Hydroxyvitamin D2[Title/Abstract]) OR 1a- Hydroxyvitamin D2[Title/Abstract]))	#4	149 117	51 254
#1 AND #2 AND #3 AND #4		113	42

her vitamin D or 25-dihydroxycholecalciferol or vitamin D or ergocalciferol or calcitriol [24] or BXL628 (a vitamin D3 analog) [25] or vitamin D3 [26] or cholecalciferol or DN-101 (a new high-dose oral formulation of calcitriol designed for cancer therapy) [22,27,28] or 1α-Hydroxyvitamin D2 [29,30] or 1a-Hydroxyvitamin D2. The supplement was vitamin D monotherapy or combined with other prostate oncology drugs such as docetaxel and doxecalciferol.

The outcomes of the studies included in the current analysis were overall survival from PC (in months), levels of PSA in the plasma after treatment (%) and the expression of VDR (increase or decrease). Study protocols or review articles, as well as studies that included injectable vitamin D supplementation or studies that used other than the abovementioned outcome measures were excluded. Additionally, editorials, abstracts, case-control studies, cross-sectional studies, case reports or series, and animal-based studies, were also excluded. A p-value of <0.05 was considered statistically significant for all the included studies.

Data extraction and methodological quality assessment

Two authors (P.S., C.S.) independently extracted the detailed information from the selected trials. Qualitative and quantitative information from each study were extracted, including author and year of study, geographic location, study size and age range, type of exposure (i.e. type of formulation), duration and dosage of vitamin D supplementation, main outcomes (as specified in the current analysis), outcome metric units and conclusions.

Two authors (P.S. and C.S.) who had received training used the appraisal instrument independently to evaluate the quality of each study. In any disagreement between raters then a third author (M.I.) was recruited. The methodological quality of the included RCTs was assessed via 11 predefined categories based on the updated Cochrane Collaboration Back review Group (BRG) method published in 2003 [31]. Each study was judged as high quality if the total score of positive responses was ≥8 / 11 and as low quality if the total score of positive responses was ≤7 / 11. Results of the methodological quality assessment are shown in Table 2.

Results

The electronic and manual searches identified 155 potential articles. 54 studies remained after duplicates were removed. After screening titles and abstracts, a total of 14 studies were selected as potentially eligible for inclusion. After reviewing and analyzing the full text articles, 6 articles were excluded due to non-eligible study designs [21, 32–35]. Furthermore, 1 study, which included men, not yet diagnosed with PC was also excluded [36]. Based on full-text review and following application of the above inclusion and exclusion criteria, a total of 8 RCTs, conducted from 2004 to 2013 were included in this analysis. The 8 RCTs studies comprised of a total of 1568 individuals aged >18 years. Results are shown in Figure 1 (PRISMA flow diagram) [37].

The geographic location the studies were conducted was diverse and dispersed worldwide. In particular, a multicenter study was conducted in different hospitals of several countries (i.e. USA, Canada, Germany, Hungary, Romania, Slovakia, Serbia and Czech Republic) [28], 5 more studies were conducted in USA [22, 24, 27, 29–30], 1 study in Canada [26], and 1 study in Italy [25] The main

Table 2. Quality assessment of the included studies [31]

Randomized Controlled Trials	Adequate randomization	Concealed treatment allocation	Similarity of groups at baseline	Patient blinded to the intervention	Care provider blinded to the intervention	Outcome assessor blinded to the intervention	Cointerventions avoided or similar	Acceptable compliance	Acceptable drop-out rate	Similar timing of the outcome assessment	Intention-to-treat analysis	Overall score*
1. (Beer, et al., 2004) (24)	Y	Y	Y	ND	ND	ND	Y	Y	Y	Y	N	7/11
2. (Colli, et al., 2006) (25)	Y	ND	Y	Y	Y	N	Y	Y	Y	Y	Y	9/11
3. (Beer, et al., 2007) (27)	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	10/11
4. (Attia, et al., 2008) (29)	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	9/11
5. (Beer, et al., 2008) (22)	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	9/11
6. (Scher, et al., 2011) (28)	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	10/11
7. (Gee, et al., 2013) (30)	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	10/11
8. (Wagner et al., 2013) (26)	Y	Y	Y	Y	Y	N	Y	Y	Y	ND	Y	9/11

Y = Yes, N = No, ND = not defined. * High quality score assessment: studies that adequately fulfil 8 or more out of 11 of the validity criteria (31) / Low quality score assessment: studies that adequately fulfil 7 or less out of 11 of the validity criteria (31)

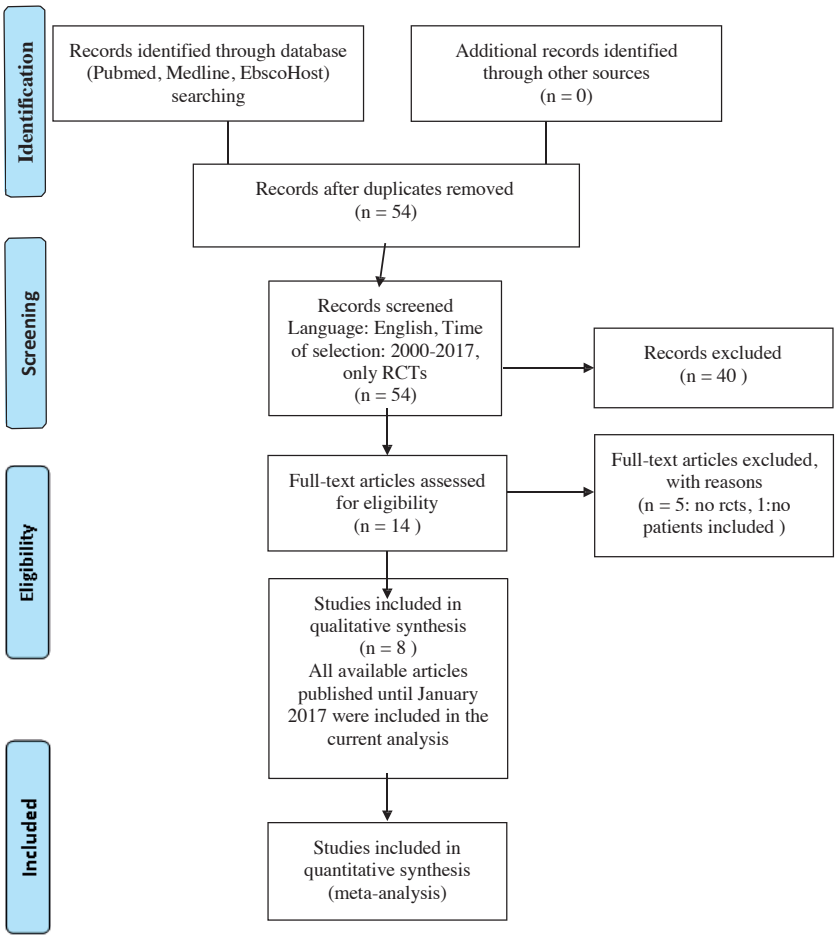

Figure 1. PRISMA 2009 Flow Diagram [37]

characteristics of the included studies are show in Table 3. The quality assessment procedure resulted in all but one [24] of the included studies being of low methodological quality [22, 25–30,]. (Table 2).

Formulation, dosage and duration of Vitamin D supplementation

4 studies included in the current review used calcitriol in doses of 0,5 μg [24] and 45 μg [22, 27–28]. Two other studies used vitamin D3 in doses of 150 μg [25] and 10–1000 μg [26], while the 2 remaining studies used 1α-hydroxy D2 in doses of 10 μg [29–30]. Duration of supplementation ranged between 28 days up to 18.3 months.

Gee, et al. (2013) and Beer, et al. (2012) had the shortest period of supplementation (28 days and 4 weeks, respectively). Moreover, Wagner, et al. (2013), Colli et al., (2006) and Beer, et al. (2008) had a moderate period of supplementation compared with the other studies (3–8 weeks, 12 weeks and 18 weeks, respectively) whereas the 3 remaining studies of Scher, et al. (2011), Attia, et al. (2008) and Beer, et al. (2007) had the longest period of supplementation (48 weeks, 17.6 months and 18.3 months, respectively).

Four out of the 8 studies used vitamin D supplementation as a monotherapy for PC [25–26, 30] (calcitriol or vitamIn D2 or Vitamin D3) while, the remaining 4 studies [22, 24, 27–29] used combination therapy of vitamin D supplements along with pharmacotherapy (i.e. docetaxel and dexamethasone).

Effect on PSA after treatment

6 studies included in the current analysis [22, 25–27, 29, 30] examined the effect of vitamin D supplementation on PSA. However, only 2 studies showed significant differences in outcome, between placebo and intervention group [26, 30] In particular, the study of Beer, et al. (2007) showed a trend towards significance for the mean time of reduction of PSA between the calcitriol and control group (2.9 months vs. 5.3 months, respectivelly, $p<0.05$). The study of Wagner, et al. (2013) showed a significant reduction in the treatment group receiving 250 μg of vitamin D3 compared with control group ($p<0.05$). Also, in the study of Gee, et al. (2013) PSA levels were significanlty reduced on the 21st day of 1α-hydroxy D2 supplementation ($p<0.05$) while the studies of Colli et al. (2006), Attia et al. (2008) and Beer et al. (2008) showed no significant effect of supplementation on PSA levels (p-value >0.05). Results of the effect of vitamin D supplementation on PSA are shown in Table 4.

Effect of supplementation on the expression of VDRs

Solely 1 study examined the effect of calcitriol on the expression of VDR, namely the study of Beer et al. (2004). The authors indicated a significant reduction on the expression of VDR in the intervention group compared with the control group ($p<0.004$).

Effect of supplementation on overall survival

3 studies [22, 27–28] in total, examined the effect of supplementation on median survival. In particular, the study of Attia, et al. (2008) did not show any significant change on the median survival between the two groups ($p>0.05$). The study of Beer, et al. (2007) demonstrated that patients in the DN-101 group (intervention group) had a hazard ratio for death of 0.67 over the placebo group ($p<0.05$). Negative results were found in the study of Scher, et al. (2011) in which the median survival of the patients was significantly higher in the control group compared with that of the treatment group ($p<0.05$). Results of the effect of vitamin D supplementation on overall survival are shown in Table 4.

Discussion

Vitamin D is a hormonal agent with pluripotent capacity and multiple applications that have either already been approved for clinical use, or remain under intensive investigation in a variety of conditions, including cardiovascular disease, oncology, endocrinology and bone health. With regard to prostate cancer - a cancer which is well known to be hormone dependent for both its local development and its preferential metastasis to bone structures - a number of studies have attempted to examine the potential benefit of vitamin D administration, usually in combination with standard of care chemotherapeutic agents, such as docetaxel and/or Doxercalciferol [38–42]. Docetaxel is a cytotoxic agent that is standard of care for patients with prostate cancer [43, 44]. Doxercalciferol (1a-dihydroxyvitamin D2, Hectorol, Genzyme), is an inactive prohormone, which undergoes hepatic conversion to its active metabolites, 1α, 25 dihydroxyvitamin D2 and 1α, 24-dihydroxyvitamin D2 [45–48]. Doxercalciferol is less calcemic than calcitriol in vivo, with acceptable tolerability and safety in humans [49].

Table 3. Characteristics of the included studies

First Author	Year	Country	Design	Population	Treatment	Control group	Duration
Beer, et al.	2004	USA		37 men > 8 years	1 caspusle calcitriol (0,5 μg) weekly	1 capsule starch	4 weeks
Colli, et al.	2006	Italy	Phase II, double blind, randomized, placebo controlled, clinical study.	119 men≥50 years	150 μg vitamin D_3 daily		12 weeks
Beer, et al.	2007	USA		250 men > 8 years	45 μg calcitriol (DN-101) on the 1st day and on the 2nd day injection of docetaxel 36 mg / m^2 with dexamethasone weekly	45 μg of placebo on the 1st day and on the 2nd day injection of docetaxel 36 mg / m^2 with dexamethasone	A cycle of 4 weeks for a mean time of 18,3 months
Attia, et al.	2008	USA		70 men > 8 years	Docetaxel 35 mg/m^2 on days 1, 8 and 15 and 1α-hydroxy D_2 10 μg from day 1 to 28 weekly	Docetaxel 35 mg/m^2, on days 1, 8 and 15 and 10 μg of placebo from day 1 to 28	A cycle of 4 weeks for a mean time of 17,6 months
Beer, et al.	2008	USA	45 men	45 μg calcitriol (DN-101) on day 1 and 36 mg / m2 docetaxel injected on day 2 with dexamethasone weekly	45 μg of placebo on day 1 and 36 mg / m^2 of injected docetaxel on day 2 with dexamethasone	A cycle of 4 weeks for a mean time of 18 weeks	
Scher, et al.	2011	198 hospitals in USA, Canada, Germany, Hungary, Czech, Romania, Slovakia, Serbia		953 men	45 μg of calcitriol (DN-101), 36 mg/m^2 docetaxel and 24 mg dexamethasone weekly	5 mg prednisone with 75 mg/m^2 docetaxel and 24 mg dexamethasone	48 weeks
Gee, et al.	2013	USA		31 men	10 μg 1α-hydroxy Vitamin D_2 daily	none	28 days
Wagner, et al.	2013	Canada		63 men	1st group: 400 IU (10 μg) of vitamin D_3 daily, 2nd group: 10 000 IU (250 μg) of vitamin D_3 daily, 3rd group: 40 000 IU (1000 μg) of vitamin D_3 daily	0 IU of vitamin D3	38 weeks

Table 4. The effect of vitamin D supplementation on PSA

Study	Results	
1. Beer, et al., 2004 [24]	ND	ND
2. Colli, et al., 2006 [25]	PSA change treatment group vs. placebo: 0.27 vs. 0,40 ng/ml ($p > 0.05$)	ND
3. Beer, et al., 2007 [27]	↓PSA >50%: 49% in patients receiving placebo and 58% in patients who received calcitriol ($p = .16$)	Overall survival: calcitriol group had a relative risk of 0.67 compared to placebo ($p = 0.04$).
	PSA mean time response: 5.3 months in patients receiving placebo and 2.9 months in patients who received calcitriol ($p = 0.06$).	Median survival: calcitriol group 24.5 months placebo group 16.4 months
4. Beer, et al., 2008 [22]	↓PSA >50%: 15 patients receiving calcitriol Stable PSA: 15 patients patients receiving calcitriol	ND
5. Attia, et al., 2008 [29]	% Change PSA: 46.7% in Vitamin D_2 group and 39.4% in the placebo group ($p = 0.560$).	Median survival in the intervention group without their cancer getting worse: 6.17 months vs. 6.20 months in the control group ($p = 0.764$).
		Median overall survival in Vitamin D_2 group was 17.8 months vs 16.4 months in the placebo group ($p = 0.383$).
6. Scher, et al., 2011 [28]	ND	312 deaths (32.7%), 138 (29.0%) in the control group and 174 (36.5%) in the intervention group with leading cause of death the prostate cancer. Median survival: Intervention group: 17.8 months + control group: 20.2 months ($p = 0.002$)
7. Wagner, et al., 2013 [26]	↓ PSA in the groups receiving 250 µg / d ($p = 0.04$) + 1000 µg IU / d ($p = 0.19$)	ND
8. Gee, et al., 2013 [30]	PSA expression Not significantly difference between groups, except for a decrease at a point in the intervention group at 21st day ($p = 0.024$)	ND

Abbreviations: PSA; Prostate Specific Antigen, ND; No Data; Significance: p<0,05,

Efficacy and safety of vitamin D supplementation in PC multimodal management

Independent of the diversity of biomarkers assessed, a well-defined positive response (i.e. reduction of PSA levels) following vitamin D supplementation was shown in the studies of Beer, et al. (2007), Beer, et al. (2008), Wagner, et al. (2013) and Beer, et al. (2004). Scher, et al. (2011) was the only study that presented negative results (i.e. reduced survival) while the remaining RCTs showed no effect. Thus, a total of 4 studies support vitamin D supplementation for PC. Three of the studies with positive results were conducted in the US while they all used calcitriol in various dosages and periods of supplementation.

A previous review article by Beer, & Myrthue (2006) aimed to examine the mechanisms of action of the VDR through clinical trials of calcitriol supplemention either as a monotherapy for intermittent periods or in combination with other drugs such as Dexamethasone, Zoledronate, Estramustine, Paclitaxel, Carboplatin. This review demonstrated that daily calcitriol supplementation accompanied by a significant dose escalation was not feasible due to the resulting adverse effects of hypercalciuria or hypercalcaemia, unlike the weekly administration of calcitriol, which allows substantial dose escalation without toxicities. While having reached significant high concentrations of supplementation, the maximum tolerated dose was not established due to pharmacological limitations. It is worth noting that the recommended dosage of weekly supplementation of vitamin D (i.e. not exceeding the RDA) as well as dosages considerably higher than the RDA did not bring forth toxicity symptoms [34]. Similarly, a more recent review article of re-examined pre-clinical and clinical studies indicates that co-administration of calcitriol

with other approved oncology drugs appears promising, while it offers a favorable approach for the optimization of the multidimensional biological and therapeutic actions of vitamin D in PC [50]. Furthermore, the use of calcitriol in combination with routine pharmacotherapy in PC patients may reduce the dosage requirements of vitamin supplementation, which in turn reduce concerns of hypercalcaemic risk.

Quantity and duration of vitamin D supplementation

Wagner, et al. (2013) study demonstrated that supplementation of 40000 IU/d (1000 μg) of vitamin D3 results in higher accumulation of metabolites of vitamin D (particularly 25(OH)D3, calcitriol, and 24,25 (OH) 2D3) within prostatic tissue. Furthermore, tissue prostate levels were shown to remain considerably high, even as their respective blood serum levels fell to zero. This indicates that vitamin D metabolism in prostate tissue is regulated independently from the vitamin's metabolism in serum.

It has been hypothesized that the increase in vitamin D prostatic tissue levels has significant and positive effect on PC progression due to its protective role against chemotherapy-induced toxicity through the cytoprotective effect of calcitriol and its precursors. Gee, et al. (2013) showed that 10 μg/day supplementation of vitamin 1α-OH-D2 for 28 days is well tolerated and can be administered with safety, with good compliance and without any indications for hypercalcemia. However, higher dosages of vitamin D3 up to 40 000 IU/d (1000 μg/d) have also been shown to be safe for patients with PC, without any adverse effects for approximately 5 weeks.

Finally, Beer, et al. (2004) showed that a high dosage of calcitriol down regulates VDR in human PC. However, this finding is not consistent with other studies possibly due to the fact that VDR expression has not yet been characterized in a large series of human PC specimens [51].

The optimal dosage of calcitriol (45 μg DN-101) may be provided from recent intravenous DN-101 administration studies that lead to increased production of calcitriol concentrations (ranging from 7–11nmol/L). Approximately 25% to 30% higher dosages that the abovementioned 45 μg per day of calcitriol, can be given with safety, if they are co-administered with dexamethasone [52–53]. However, in the study of Scher et al. (2011), patients underwent 28-day dosing cycles of 45 μg oral DN-101 for 21-day cycle the results were negative. The authors state that this might be due to either weekly docetaxel dosing or the DN-101 therapy. However, design limitations, such as heterogeneity in ethnic origin of the sample population may also have affected the outcome of the study.

It appears that a dosage as high as 1000 μg per day - i.e. in quantities much higher than the RDA - results in an increase in metabolites of vitamin D in cancerous prostate tissue, which may affect PC development and benefit prognosis [26]. For small periods of time (i.e. 4–5 weeks) this quantity appears safe without any serious adverse effects on health. Data for higher periods of administration are not – to the best of our knowledge – currently available.

Vitamin D effect on Specific Prostate Antigen (PSA)

In the Wagner, et al (2013) study, despite the fact that reductions observed in serum PSA were small and occurred after a very short duration of therapy, oral administration of vitamin D3 reduced the rate of PSA level increases in PC patients. These results also indicate that a high dosage of vitamin D3 (≥10 000 IU / day) for short periods of administration should be further investigated as a therapeutic option for managing serum PSA levels. However, vitamin D3 supplementation (i.e. 4000 IU/day) has been shown to slow down the progression of PC, without significant changes in PSA levels [54]. PSA level reduction may be achieved through higher calcitriol supplementation (at 10 000 to 40 000 IU/day), thus ascertaining a potential clinical benefit.

On the other hand, studies, such as the Gee, et al (2013) RCT using, simultaneous supplementation of calcitriol (DN-101) alongside docetaxel, did not conclude to significant improvements on PSA levels [27, 30]. These results may be explained either by the fact that vitamin concentrations were insufficient in prostate tissue, the exposure time was not sufficient in order for a significant result to be obtained or that the potency of the vitamin D analog given (1α-OH-D2), with its pre-described minimal biologic activity, was deficient in human prostate. The study by Attia, et al (2008) further indicated that even if D2 is co-administered with other drugs - which have shown in the past to aid the activity of calcitriol – no significant effect on PSA levels is evident. Both studies with negative findings (i.e. Gee, et al. (2013) and Attia et al (2008)) are of high methodological quality and at the same time are the sole two RCTs in which vitamin D2 was administered in low dosages and for the same duration of time (i.e. 28 days). This may signify either that this type of vitamin D is not appropriate for this group of patients or that the dosage of vitamin D given is low for any significant therapeutic effect to be evidenced. The period of supplementation was medium compared with the other studies, a fact that is probably unrelated to the negative results observed particularly since other studies, with similar duration of supplementing vitamin D, indicate positive results [26].

According to the results of the current review, studies differ in the amount, type and duration of vitamin D supplementation, as well as their effect on PSA levels. In 2 studies [29,30], 10 μg of D2 Hydroxyvitamin were administered for 28 days, with no significant results. Vitamin D3 resulted in a positive response solely when administered in high dosages (>10 000 IU) and for a comparatively medium period of time. The most popular type of vitamin D used in these studies was calcitriol but there are differences in amount and duration of supplementation that lead to heterogeneity of study results. This may mean that the duration needs to be matched to the appropriate dosage, i.e. a high dosage (250–1000 μg) requires small duration of administration (3–8 weeks), while a small dosage (45 μg) may be administered for a longer period of time (18,3 months). Future research could provide algorithms for ideal vitamin D dosages to be matched to optimal duration of supplementation according to individual patient needs.

As a biomarker for the diagnosis of prostate tumors, prostate specific antigen (PSA) is currently the most commonly used, despite several disadvantages of its use [13]. The widespread use of PSA testing for the early detection of PC has potentially resulted in a shift in the epidemiology of the disease such that an increasing number of men are diagnosed and treated with clinically localized disease at a younger age. [55–56]. PSA also remains a valuable tool in the monitoring of the disease following treatment in patients with localized or with advanced PC [57].

The cellular and molecular pathways involved in the effect of vitamin D on PSA levels, are not well delineated and require further investigation. In in vitro studies, calcitriol induces differentiation of a number of cell types as well as the normal prostate and CaP cell lines [58–61]. Calcitriol treatment of LNCaP cells, a human PC cell line, up-regulates the expression of the androgen receptor (AR) and increases secretion of prostate-specific antigen (PSA). This indicates that calcitriol may initiate differentiation of PC cells, thus decreasing cellular proliferation [62].

Expression of vitamin D receptors (VDR)

VDR, the specific nuclear receptor protein, is expressed in human prostatic cells. A series of experiments reveal that VDR mediates the influence of 1,25(OH)2D3 on the growth, differentiation [63, 64], and apoptosis [65] of prostatic cells.

The Beer, et al. (2004) study showed a considerable reduction in the expression of VDR in the calcitriol-supplemented group compared with the placebo group. The reduction in the number of adenocarcinoma cells that express VDR in patients in the calcitriol intervention group was modest. However, to the best of our knowledge this is currently the only RCT that investigates the effect of vitamin D supplementation on the expression of VDRs.

Preclinical research provides conflicting results regarding the effect of calcitriol on VDR expression. Many in vitro experiments that examined the expression of VDR after a small duration (≤24 hours) of calcitriol exposure show an increase in VDR concentrations. However, the expression of VDR has not been previously determined in large enough samples of human PC and therefore there can be no definite conclusion as to whether vitamin D enhances or not the expression of VDR [24].

Gene polymorphisms of the VDR gene have been reported to be of significant relevance to cancer risk in many different populations [66–75], altering the response of the organism to vitamin D supplementation. Perhaps in future studies of vitamin D supplementation, VDR expression and sequence variations will be assessed in PC patients, thus clarifying the role of VDR in PC pathogenesis.

Overall Survival

No difference in survival was recorded after vitamin D administration in the Attia, et al. (2008) study. A limitation of this study was that it used PSA levels as a measure for therapeutic responsiveness, which could have confounded the results since it does not constitute a valid marker for survival prediction. On the contrary, Beer et al (2007) showed that the addition of DN-101 in docetaxel correlated with a reduced risk of death (approximately 1/3 less in the intervention group). If these results could be ascertained in a clinical trial phase III, then this would be a significant finding for PC therapy, even further reducing the relative mortality risk of 0,76–0,8 shown in 3-week clinical trials of docetaxel chemotherapy, using mitaxandrone and prednizone as control therapies [38]. On the contrary, Scher, et al. (2011) showed a negative effect of calcitriol treatment on the overall survival. Although, all 3 studies [27–29] were of high methodological quality as assessed in the current analysis, other factors may have contributed to the abovementioned controversial findings. For example, 2 studies, namely Beer et al (2007) and Scher et al (2011), used the same dosage, type of supplementation and pharmacotherapy, yet the population size and duration of supplementation were different. The larger size of population (953 vs 250) and the shorter duration of supplementation (48 weeks vs. 4 weeks) in the study by Scher et al. (2011) compared with the Beer et al (2007) study, may indicate that 45 μg of calcitriol has no beneficial effect on the overall survival of patients with PC. It is could be assumed that longer periods of calcitriol treatment (up to 18 months) may lead to positive results.

Strengths and Limitations

Strengths of this review include the exclusive inclusion of RCTs, as well as the high methodological quality of the majority (7 out of 8) of the studies included [31].

The limitations vary according to the studies included. Only 2 of the included studies make a reference to the baseline levels of vitamin D in serum, which makes it impossible to determine if the levels of serum vitamin D before the intervention could have affected treatment outcomes. Regarding the expression of VDR, solely 1 study investigated its involvement in treatment outcomes, which makes it impossible to draw accurate conclusions. Additionally, vitamin D was not administered on its own but rather as a combination treatment with other drugs that are indicated for PC treatment. These may also have affected, to some extent, the action and outcome of vitamin D studies in PC. Also, RCTs were few in number, while heterogeneity was evident in measures of exposure and outcomes. Finally, a meta-analysis could not be performed since the outcomes were not measured in a similar enough manner to be mathematically combined.

Future perspectives

Further to dosage, period of administration and type of vitamin D supplements, the route of administration is also important in clinical trials of therapeutic agents. Novel routes such as nasal, intra-dermal administration, sublingual and buccal should be explored in supplement bioavailability studies. In effect their therapeutic effect must be viewed in the future in such context [74–75].

Besides nationality and age differences, genetic makeup may interfere with the results of the above-mentioned studies (i.e. due to polymorphisms in VDR [76]. Personalized medicine and nutrigenomics – nutrigenetics should for this reason be taken into consideration in future clinical trials assessing the efficacy of therapeutic dietary supplements [77]. Polymorphisms of gene variants (e.g. Cytochrome P450, glutathioneglutathione-S-transferases) that are involved in prostate carcinogenesis have been studied, particularly those modifying the bioavailability, metabolism, and activity of dietary constituents such as vitamin D. Furthermore, genes that have a role in influencing other mechanisms of prostate carcinogenesis, such as those involved in DNA replication and repair as well as those involved in the production of sex hormones, have also been studied and may lead to accurate and effective treatments through clinical trials in the near future [78]. Bioinformatics and biostatistics tools will prove increasingly important in nutrigenetic and nutrigenomic studies. Also, single nucleotide polymorphisms, chromosomal rearrangements and epigenetic changes may shed light into the controversy of data presented in clinical trials of vitamin D supplementation for PC [79]. Large international cohorts may indicate individual nutrient-gene interactions and nutrient-gene-gene interactions for the study of PC development and therapeutic efficiency of supplemental vitamin D.

Many pharmacological and dietary supplement combinations exhibit therapeutic potential for various types of cancer [80]. It is expected that future research will target the need for well-designed clinical trials in order for effectiveness and safety to be ascertained.

This work has been conducted at European University Cyprus, Nicosia, Cyprus. E-Mail the corresponding author for reprints.

Conflict of Interest

The authors of this article have no conflict of interest to declare.

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