5-10-2024

The effects of vitamin D supplementation on prostate cancer

Grier Cosby
Mississippi State University, gcosby777@outlook.com

The effects of vitamin D supplementation on prostate cancer

By

Grier Cosby

Approved by:

Amanda G. Conrad (Major Professor)
Terezie Tolar-Peterson
Rahel Mathews
Wen-Hsing Cheng (Graduate Coordinator)
Scott T. Willard (Dean, College of Agriculture and Life Sciences)

A Thesis
Submitted to the Faculty of
Mississippi State University
in Partial Fulfillment of the Requirements
for the Degree of Master of Science
in Food Science, Nutrition, and Health Promotion with a Concentration in Nutrition
in the Department of Food Science, Nutrition and Health Promotion

Mississippi State, Mississippi

May 2024

Name: Grier Cosby

Date of Degree: May 10, 2024

Institution: Mississippi State University

Major Field: Food Science, Nutrition, and Health Promotion

Major Professor: Amanda G. Conrad

Title of Study: The effects of vitamin D supplementation on prostate cancer

Pages in Study: 65

Candidate for Degree of Master of Science

ABSTRACT

This systematic review's goal is to evaluate the efficacy of vitamin D supplementation in helping to manage the nutritional needs of patients diagnosed with prostate cancer. A systematic literature search following the PRISMA guidelines using Scopus, PubMed, and Cochrane databases was conducted to review randomized controlled trials and interventional studies up to 2023. The search strategy targeted randomized controlled trials and intervention studies. The selection process involved screening for study characteristics (study design), participant demographics (prostate cancer patients receiving treatment), intervention details (vitamin D assessment methods, dosages), outcome measures (progression, prognosis, quality of life), and risk estimates (hazard ratios, odds ratios, relative risks) along with covariates adjusted for in the analysis. Data analysis and synthesis included studies assessing vitamin D supplementation's impact on prostate-specific antigen (PSA) levels, tumor progression, osteomalacia, overall survival rates, and quality of life assessments. The literature search yielded a total of 3575 documents. After a preliminary screening of titles and abstracts, 34 full-text studies were examined. In total, nine studies were determined to meet the inclusion criteria. The findings of

nine studies suggest a modest but significant association between vitamin D supplementation, reduced PSA levels, slower progression of localized prostate cancer, and improved bone loss. Due to the various treatment options, the overall effects of supplementation on advanced prostate cancer and overall survival were inconclusive. However, this research highlights the potential role of vitamin D in prostate cancer management.

DEDICATION

To my friends and family

ACKNOWLEDGEMENTS

I would like to extend my deepest gratitude to Dr. Conrad, Dr. Mathews, and Dr. Tolar-Peterson for their invaluable guidance, support, and expertise throughout my academic journey. Their dedication and encouragement have been pivotal in my growth and achievements. I am also immensely thankful to my friends and family, who have given me unwavering support and love. A special mention goes to my dad, whose wisdom, patience, and belief in me have guided this academic journey. This accomplishment is not just mine, but a reflection of all the support and faith bestowed upon me by these remarkable individuals.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER I

INTRODUCTION

The research focusing on vitamin D and prostate cancer has progressed significantly over the past two decades. It encompasses a range of studies, from clinical trials in various populations to observational studies considering environmental factors such as sunlight exposure. This research is especially true for cancers that rely on metabolic mechanisms like those supported by vitamin D through the VDR, as well as understanding how calcitriol affects metabolic balance (Deeb et al., 2007a). Given that targeted cancer therapies often aim to disrupt signaling pathways enabling cancer cell proliferation, the role of active calcitriol in the VDR pathway has become a focal point of investigation. Vitamin D could help fight cancer by inhibiting cell growth, promoting cell death, and limiting the formation of new blood vessels. It can also enhance the anticancer properties of some drugs (Deeb et al., 2007b). The primary function of calcitriol is to bind to the nuclear vitamin D receptor (VDR), which then heterodimerizes with the retinoid X receptor and binds to vitamin D responsive elements located near target genes (Muscogiuri, 2020). Emerging studies on vitamin D analogs targeting cancer cells to hinder their proliferation also underscore the growing interest in understanding vitamin D's role within the individual patient's physiology (Duffy et al., 2017). Overall, epidemiologic studies have produced mixed results, but there is some indication that severe vitamin D deficiency may increase the risk of clinically significant prostate cancer. Laboratory investigations have provided substantial evidence on the potential of vitamin D receptor (VDR)

ligands to induce growth arrest and promote apoptosis in various cancer models. Due to the presence of hundreds of vitamin D responsive genes, various mechanisms have been proposed to explain these observations (Christine M. Barnett & Tomasz M. Beer, 2011).

Prostate cancer is the second most common cancer among men. The good news is that preventative measures can be taken due to the long period of time it takes to develop, the availability of tumor markers, and its high incidence. However, there is limited insight into the basic mechanisms of vitamin D's role in the development of prostate cancer, despite studies on vitamin D levels in serum and prostate tissue, as well as the observed activity of vitamin D enzymes and genetic changes (G. Marusic et al., 2013). It is commonly known that vitamin D is important for maintaining strong bones. However, we have yet to fully understand all its crucial physiological effects. Low levels of vitamin D have been linked to the development of numerous diseases, including cardiovascular disease, hypertension, cancer, and autoimmune-based pathologies like multiple sclerosis. Vitamin D deficiency has been linked to not only prostate cancer but also to colorectal cancer. Moreover, there is evidence to suggest that it plays a role in skin and breast cancers. It has been observed that elevated levels of vitamin D can lead to worse outcomes in cases of breast, esophagus, and pancreatic cancer (Naomi Smith & Alejandro Nolazco, 2013). Vitamin D has been found to have several biological responses in various human prostate cancer cell lines and in primary cultures derived from normal, benign prostatic hyperplasia (BPH), and prostate cancer. These biological responses include growth inhibition and PSA stimulation. Vitamin D is known to be an important cellular modulator of growth and differentiation, besides being a regulator of calcium homeostasis. It promotes cellular maturation and is anti-proliferative. Therefore, it has the potential to be beneficial in treating various malignancies, including prostate cancer. Although the ultimate role of vitamin D in prostate

cancer is yet to be determined, caltitriol may prove useful in chemoprevention and/or differentiation therapy. More research is necessary to determine if vitamin D can be used as a treatment for prostate cancer. However, initial data suggests that it may have potential therapeutic benefits (David Feldman et al., 1995). This review aims to enhance understanding of this field's current scope of knowledge.

CHAPTER II

LITERATURE REVIEW

What is Vitamin D

The vitamin D group of fat-soluble secosteroids has numerous biological effects, including increased intestinal absorption of calcium, magnesium, and phosphate (Bikle, 2014). Vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol) are the two most crucial compounds in this class secosteroids for people. Vitamin D3 (cholecalciferol), which is synthesized in the lower layers of the skin's epidermis in response to UVB light from the sun or UVB lamps. Vitamin D3 (ergocalciferol) is a form of vitamin D that occurs naturally in food and is also sold as a supplement (Bikle, 2014). Vitamin D3 deficiency due to intestinal malabsorption or liver disease can be prevented or treated by taking vitamin D in the supplemental form (Bilezikian et al., 2021). Vitamin D also plays a crucial role in maintaining healthy bones and teeth by regulating calcium and phosphate levels in the body. It also supports immune function and helps reduce the risk of chronic diseases such as osteoporosis and certain types of cancer (Holick, 2006). There are studies that illustrate that vitamin D may benefit mental health as well as physical health, affecting mood and cognitive performance (Kang et al., 2021). As a result, vitamin D is more than just a nutrient; it also plays a key role in maintaining both our physical and mental health (Bikle, 2014).

Incidence and Prevalence of Prostate Cancer

Prostate cancer predominantly affects older men worldwide, with varying incidence rates across different regions. The disease's occurrence ranges from 6.3 to 83.4 per 100,000 individuals, with Northern Europe having the highest rates and South-Central Asia having the lowest (Giona, 2021). Prostate cancer is notably prevalent among men, and its exact etiology and risk factors continue to be the subject of ongoing research. Studies have indicated a correlation between a Western diet high in saturated fats and both the incidence and progression of prostate cancer(Matsushita et al., 2022). Recent research from the American Cancer Society highlights growing incidence rates in the United States, marking a shift from a previous period of decline ("Rising Prostate Cancer Incidence Rates," 2023). Globally, the last decade has seen a 66% increase in prostate cancer occurrence, making it the most frequently diagnosed cancer among men in 103 countries (Mucci et al., 2017). In the United States, prostate cancer is the most prevalent cancer in males, other than skin cancer, with about one in six men diagnosed during their lifetime (Darves-Bornoz et al., 2014).

Incidence and Prevalence of Low Vitamin D Levels

Despite the ability of the skin to produce vitamin D with minimal sunlight exposure, vitamin D deficiency is still widespread, particularly among the elderly in the U.S., Canada, and Europe. It has been estimated that 20 – 100% of this demographic is vitamin D deficient, often due to insufficient dietary intake or lifestyle factors (Holick et al., 2011). Genetic factors can also influence an individual's vitamin D status. The Institute of Medicine (IOM) recommends specific serum levels of 25(OH)D to define vitamin D deficiency as less than 20 ng/mL and insufficiency as 21–29 ng/ml. To optimize bone health and muscle function, older adults should consume at least 600 to 800 IU/d of vitamin D, as per the Endocrine Society's recommendations, though

whether these amounts suffice for other non-skeletal health benefits, including cancer prevention, is still being debated (Holick et al., 2011). The serum concentration of 25(OH)D is a crucial clinical marker for monitoring vitamin D status, with serum 25(OH)D having a biological half-life of 2–3 weeks. The Institute of Medicine advises that a serum 25(OH)D concentration of more than 50 nmol/L is appropriate for healthy bone and mineral metabolism (DiMeglio & Imel, 2019). Table 2.1 provides the recommended intake for calciferol. And Table 2.2 Provides the recommended serum calcidiol levels.

Table 2.1 Recommended Intake for Calciferol.

Age Group	**Male**	**Female**	**Pregnancy**	**Lactation**
0-12 months	10 mcg (400 IU)	10 mcg (400 IU)		
1–13 years	15 mcg (600 IU)	15 mcg (600 IU)		
14–18 years	15 mcg (600 IU)	15 mcg (600 IU)	15 mcg (600 IU)	15 mcg (600 IU)
19–50 years	15 mcg (600 IU)	15 mcg (600 IU)	15 mcg (600 IU)	15 mcg (600 IU)
51–70 years	15 mcg (600 IU)	15 mcg (600 IU)		
>70 years	20 mcg (800 IU)	20 mcg (800 IU)		

(*Office of Dietary Supplements - Vitamin D*, 2024)

Table 2.2 Recommended Serum Calcidiol Levels.

Serum Level (nmol/L)	Equivalent Range in ng/ml	National Academy of Medicine Description	Bone Health Outcomes
<30 nmol/L	<12 ng/ml	Persons with levels in this range are at risk of deficiency relative to bone health outcomes	Severe deficiency
Between 30-50 nmol/L	Between 12-20 ng/ml	Some, but not all, persons in this range are at risk of deficiency relative to bone health outcomes	Deficiency
Between 50-75 nmol/L	Between 20-30 ng/ml	Most, but not all, persons with levels in this range are sufficient relative to bone health outcomes	Some refer to this range as insufficiency; others contend this range is sufficiency.
>75 nmol/L	>30 ng/ml	Persons with levels in this range do not consistently have an increased benefit relative to bone health outcomes	Sufficiency
Above 125 nmol/L	Above 50 ng/ml	Levels in this range may be cause for concern	–

(Kahwati et al., 2018)

Research on Vitamin D and Cancer

Vitamin D, obtained through dietary sources, supplements, or synthesized in the skin upon sunlight exposure, is increasingly recognized for its effects beyond traditional functions. Emerging evidence suggests that vitamin D may influence various biological processes in cancer development, such as cell proliferation, differentiation, and apoptosis, due to the active calcitriol effects on VDR (Seraphin et al., 2023). This complex nature of vitamin D has fueled research into its potential impact on prostate cancer incidence, aggressiveness, and outcomes. Vitamin D, as a fat-soluble and prohormone, is known for its roles in metabolism but has also emerged as a potentially influential factor in cancer prevention and progression (Carlberg & Muñoz, 2022; Deeb et al., 2007a).

Epidemiological studies have suggested that vitamin D deficiency may contribute to the etiology of various cancers, including prostate, breast, and colon. Various tissues and immune cells, including those of the brain, prostate, breast, and colon, possess vitamin D receptors (VDR) and respond to the active form of calcitriol. Additionally, some of these cells can convert calcidiol to its active form, thanks to the enzyme 25-hydroxyvitamin D-1α-hydroxylase. Calcitriol exerts a broad regulatory effect on cells, not limited to those involved in managing calcium levels. Through binding with the VDR, vitamin D influences cellular functions by inducing differentiation and apoptosis, and inhibiting cell proliferation, angiogenesis, and the potential for metastasis. Consequently, vitamin D is being investigated for both the etiology and treatment of certain cancers that have VDR's (Gupta et al., 2011).

Preclinical research indicates that calcitriol, the active metabolite of vitamin D, and vitamin D analogs may serve as anticancer agents due to their antiproliferative effects, ability to activate apoptotic pathways, and inhibition of angiogenesis (Carlberg & Muñoz, 2022). Beyond its traditional role, vitamin D may have implications in preventing chronic diseases such as cardiovascular disorders and metabolic conditions that often accompany cancer treatments. The presence of vitamin D receptors in various tissues throughout the body contributes to the regulation of a wide range of biological functions. Hence, understanding and maintaining appropriate levels of this essential prohormone is critical not only for preventing chronic diseases like cancer but also for their treatment.

Previous Studies on Vitamin D and Prostate Cancer

Previous studies have examined the connection between vitamin D and prostate cancer. A review of literature has shown that the focus has changed over the past two decades from supplemental vitamin D to laboratory-modified vitamin D analogs for achieving desired results.

A study titled "The Effect of Vitamin D Supplementation on Prostate Cancer: A Systematic Review and Meta-Analysis of Clinical Trials" investigated the effects of vitamin D supplementation for prostate cancer patients. However, the study only covers the effects on prostate-specific androgen (PSA). This study did not find any convincing evidence that vitamin D supplements had a positive impact on serum PSA levels, PSA response proportion, or mortality in patients with prostate cancer. Although this study is limited to PSA outcomes and fails to consider other benefits of supplementation. Historically, vitamin D has been considered potentially protective against the development of prostate cancer, based on early observations of higher cancer risk in individuals with lower serum vitamin D levels. However, this study suggests that vitamin D supplementation does not effectively treat prostate cancer. The study outlines various mechanisms by which vitamin D works, such as influencing cell proliferation, gene expression, and immune response. Still, the study's findings do not confirm these beneficial effects in the context of prostate cancer with the outcomes measured for PSA levels. It was also difficult to assess the benefits of taking vitamin D during treatment for other reasons such as limiting inflammation and preserving bone density. The study also highlighted significant limitations in existing research, such as the lack of reporting on participants' baseline and post-intervention vitamin D status, which could influence the outcomes of supplementation. Additionally, reliance on before-after studies, which may offer misleading results compared to the more robust evidence provided by RCTs, is mentioned (Shahvazi et al., 2019).

Importance of Vitamin D in Human Health

Vitamin D, or the "sunshine vitamin," is indispensable for overall health and well-being. Formed in the skin through sunlight exposure and obtained from certain foods and supplements, it plays a crucial role in many bodily functions as stated previously. Beyond its primary task of

regulating calcium and phosphate levels for healthy bones, vitamin D extends its influence on the immune system, muscle function, and cardiovascular health. Some of the more recent research has further unveiled its involvement in reducing inflammation, aiding cell growth, and potentially offering therapeutic benefits in various diseases. This advancing research makes understanding and maintaining adequate vitamin D levels not just a matter of bone health but a cornerstone in managing human health (Calcium et al., 2011).

Through its interaction, the active form of vitamin D 1,25(OH)2D, also referred to as calcitriol, which is found in the blood and is primarily regulated by the kidneys, is accountable for maintaining calcium-phosphate homeostasis, which is one of the most important practical functions when treating nutrition-related complications in prostate cancer as patients can develop hypokalemia as the disease progresses. Vitamin D can improve the efficiency of the intestinal absorption of dietary calcium. In addition, vitamin D receptors (VDR) can be found throughout the human body, and vitamin D performs various functions unrelated to calcium. It is clear that vitamin D is significantly connected to the health of the vascular, immune, nervous, and muscular systems (Janoušek et al., 2022). Vitamin D is also unique among vitamins that the body needs due to its dual source. Because it develops in the skin when exposed to sunlight, specifically UVB rays, and it can also be ingested in food or supplements. The body's ability to produce vitamin D through sunlight depends on several factors, including geographic location, time of day, skin pigmentation, and sunscreen or protective clothing. These variables often make it challenging to obtain sufficient sun exposure, especially in higher latitudes, during winter months, or for individuals with darker skin tones who require more prolonged sun exposure to synthesize the same amount of vitamin D. Dietary sources, such as fatty fish, egg yolks, and fortified foods, offer an alternative. However, not all populations can consume these in adequate

quantities, leading to a reliance on supplements. The Recommended Dietary Allowance (RDA) for vitamin D, set to ensure bone health and overall well-being, can be challenging to meet through sunlight and diet alone, particularly for those living in areas with limited sun exposure, dietary restrictions, and various health needs. This complexity in obtaining adequate vitamin D highlights the need for awareness and potentially tailored strategies to ensure sufficient levels for optimal health (Calcium et al., 2011; Janoušek et al., 2022). Inadequate vitamin D levels can lead to a spectrum of health issues, while over-supplementation carries its risks. Deficiency in vitamin D is primarily known for causing bone-related problems like rickets in children and osteoporosis in adults due to impaired calcium absorption. However, its deficiency also extends to more subtle impacts on immune function, increasing susceptibility to infections and chronic diseases like diabetes and cardiovascular ailments. On the other hand, excessive vitamin D intake, typically due to over-supplementation, can lead to hypercalcemia a condition where calcium levels in the blood become too high. Hypercalcemia can result in a range of symptoms, including nausea, weakness, frequent urination, and, in severe cases, kidney stones or renal failure. With the complex health needs of the population, it is essential to consider drug and nutrient interactions that can cause imbalances such as hypercalcemia or toxicity. The delicate balance of maintaining adequate vitamin D levels is crucial, as both deficiency and excess can have significant consequences for overall health (Calcium et al., 2011; Janoušek et al., 2022). Although vitamin D is known for its link with bone fractures and bone diseases, recent studies revealed that vitamin D and its analogs have revealed many pharmacological actions covering the regulation of cell growth, inhibition of inflammation, and improvement of neuromuscular function and immune function. Moreover, vitamin D and its analogs are reported to have a role in different types of cancers, skin diseases, diabetes mellitus, and infections caused by different

bacterial and viral pathogens, including SARS-CoV-2 (Alaraj et al., 2022). Vitamin D stands as a pivotal nutrient in the realm of health and well-being. Its quintessential role in maintaining bone strength and calcium homeostasis is well-established, but its benefits extend far beyond. Vitamin D is critical in modulating the immune system, reducing inflammation, and potentially influencing mood and mental well-being. Emerging research highlights its significance in reducing the risk of chronic diseases. Its potential to enhance muscle function and combat infections adds to its impressive profile. As we unravel the multifaceted roles of this essential vitamin, it becomes clear that maintaining adequate vitamin D levels is a crucial component of a holistic approach to health, underscoring its importance as a cornerstone of preventive healthcare and therapeutic strategies (Passeri & Giannini, 2023).

Dietary Sources of Vitamin D

Dietary vitamin D and vitamin D produced by the skin are biologically inactive. The hydroxylation of two protein enzymes activates it, the first in the liver and the second in the kidneys. Once activated the prohormone vitamin D, is considered a hormone calcitriol, which exerts its effects via multiple nuclear receptors (*Office of Dietary Supplements - Vitamin D*, 2024). Vitamin D appears in both ergocalciferol (Vitamin D2) which is the main source found in plants and cholecalciferol (vitamin D3) which can be found in animal products such as in dairy and cod fish oil. Ergocalciferol, which is made in yeast and fungi in the presence of UVB light exposed to provitamin D2, some plants contain vitamin D2 if they have been introduced to fungi (Jäpelt & Jakobsen, 2013). The two types of vitamins D2 and vitamin D3 differ only by their side chains. Both cholecalciferol and ergocalciferol can be obtained through dietary sources and dietary supplements (Bilezikian et al., 2021). Below is a figure depicting the conversion of

vitamin D from either cholecalciferol or ergocalciferol into the active from calcitriol [1,25(OH)2D]. Below is a brief list of foods that are high in vitamin D.

Figure 3.1 Foods high in vitamin D.

Food Item	Portion	Calories	Vitamin D (IU)
Protein Foods			
Rainbow trout, freshwater	1 ounce	47	215
Salmon (various)	1 ounce	~40-60	128-190
Light tuna, canned	1 ounce	56	77
Herring	1 ounce	57	61
Sardines, canned	1 ounce	59	55
Tilapia	1 ounce	36	42
Flounder	1 ounce	24	39
Dairy and Fortified Soy Alternatives			
Soy beverage (soy milk), unsweetened	1/2 cup	40	60
Milk, low fat (1 %)	1/2 cup	51	59
Yogurt, plain, nonfat	4 ounces	69	58
Yogurt, plain, low fat	4 ounces	77	58
Milk, fat free (skim)	1/2 cup	42	58
Kefir, plain, low fat	1/2 cup	52	50
Cheese, American, low fat or fat free, fortified	1/2 ounce	52	43
Vegetables			
Mushrooms, raw (various)	1/2 cup	~8-10	57-555
Fruit			
Orange juice, 100%, fortified	1/2 cup	59	50
Other Sources			
Almond beverage (almond milk), unsweetened	1/2 cup	18	54
Rice beverage (rice milk), unsweetened	1/2 cup	57	51

(*Food Sources of Vitamin D | Dietary Guidelines for Americans*, 2024)

Recommended Diet for Prostate Cancer

Several studies have suggested that adopting a low-fat diet can potentially benefit prostate cancer patients in terms of disease progression and survival rates. Research has shown that incorporating healthy dietary patterns, such as a diet high in fiber and soy and low in fats, can significantly improve metabolic outcomes in prostate cancer patients who are undergoing androgen-deprivation therapy (ADT). By consuming a diet rich in fruits and vegetables, patients experience a reduction in inflammation and oxidative stress, which are known to be risk factors

for cancer progression. Additionally, limiting the intake of fats can help regulate hormone levels and prevent cancer cells from growing rapidly (Mukhtar, 2022). Prostate cancer patients have also been found to benefit from a periodic fasting mimicking diet (FMD), which is low in calories, sugars, and proteins but high in unsaturated fats. This kind of diet has been shown to improve metabolic health factors which is concern for anyone diagnosed (Wang et al., 2022). Studies have demonstrated that statins, a class of drugs commonly used to lower cholesterol levels, can have a positive impact on prostate cancer outcomes by decreasing PSA levels. However, research has also shown that adopting dietary interventions that lower cholesterol levels can lead to similar effects, including reductions in serum PSA levels and estimated risk of developing prostate cancer (Chi et al., 2022). The findings strongly suggest that adopting a low-fat diet can significantly improve disease progression and increase survival rates among prostate cancer patients.

Vitamin D Synthesis in The Skin

The production of vitamin D can be accomplished both from sunlight and food sources. Vitamin D produced in the skin with the presence of sunlight UVB (ultra-violent B) is rate limiting depending on the clothing worn, time of year, geographical occasion, and the presence of melanin in the skin. The rate of production is at its highest when the skin has not burned and damaged the cells in the range of 290–315 nm (Tian & Holick, 1995). Continued metabolism of vitamin D either from sunlight or food sources to the circulating forms that are used to determine exposure calcidiol [25(OH) D] and the active hormonal form of calcitriol (1,25(OH)2D) happens in the liver. Vitamin D inactive (25(OH)D) into active hormonal calcitriol (1,25(OH)2D) can happen in various organs and tissues such as the prostate, breast, parathyroid gland, intestinal epithelium, skin cells, and cells of the immune system (Bikle, 2014).

Vitamin D2 unlike D3 is made only by plants. It is different from vitamin D3 because it has a methyl group at C24 and a double bond at C22–C23 (Jäpelt & Jakobsen, 2013). Vitamin D3 that is produced in the skin from 7-dehydrocholesterol (7DHC), occurs in the process of making cholesterol and this step in the synthesis is not considered an enzymatic reaction. When exposed to UVB light (290–315 nm), the ring in the C9–C10 position goes through an electrocyclic rearrangement, which makes pre-vitamin. Once pre-vitamin D3 is made, it changes into vitamin D3 through a process called thermal isomerization, in which hydrogen moves from C19 to C9. This overall reaction is irreversible and as a result both Pre-Vitamin D3 and Vitamin D3 coexist (Tian & Holick, 1995). The amount of vitamin D3 made depends on the amount of 7DHC, which in turn depends on the activity of 7 dehydrocholesterol reductase (DHCR7). This is the rate-limiting step in skin production. The enzyme DHCR7 helps turn 7DHC into cholesterol in a way that can be reversed as described in the Kandutsch-Russell cholesterol pathway (Kandutsch, 1962).

The final enzymatic reaction mediated by 7-dehyrocholesterol reductase that converts 7-DHC to cholesterol is regulated by several factors, including vitamin D and cholesterol, which enhance its degradation and allows for increased levels of 7-DHC to be converted to vitamin D. This regulation ensures a balanced production of cholesterol and vitamin D in the body. Additionally, the activity of 7-dehyrocholesterol reductase can be influenced by other factors such as hormonal signals and dietary intake, further modulating the conversion of 7-DHC to cholesterol and vitamin D (Prabhu et al., 2016). Figure 2.1 provides an overview of the synthesis of vitamin D into the active form calcitriol.

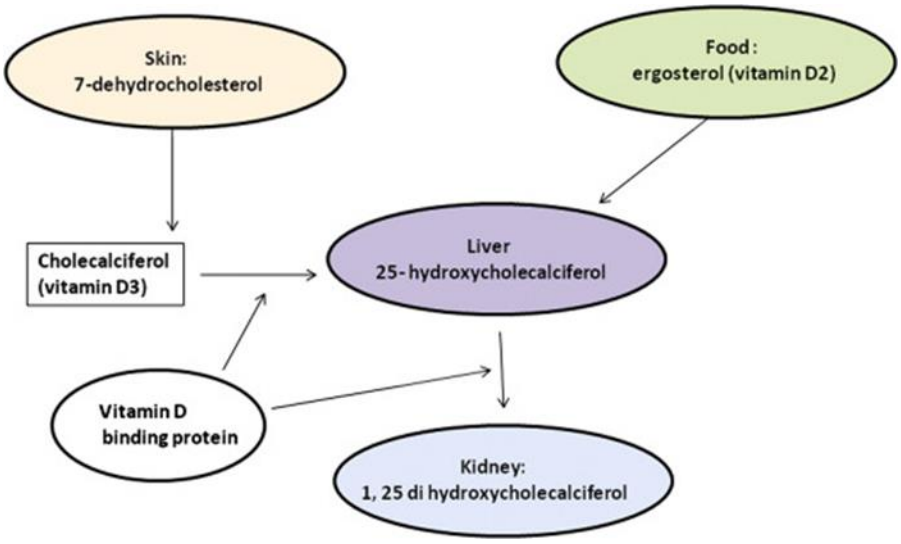

Figure 2.1 Overview of the Synthesis of Vitamin D Into the Active From Calcitriol (*Vitamin D Metabolism - an Overview | ScienceDirect Topics*, 2023)

Mechanisms By Which Vitamin D Regulates Bone Metabolism

Vitamin D is essential for maintaining healthy bones as it helps to regulate the levels of minerals in our body. More specifically, it plays a crucial role in the regular metabolism of our bones by facilitating the absorption of calcium and phosphorus by the intestine, two important minerals that are necessary for the formation and maintenance of strong bones. Vitamin D levels regulate the production of the active form of vitamin D (1,25(OH)2D) by increasing the expression of 1α-hydroxylase and decreasing the expression of 24-hydroxylase (Charoenngam et al., 2019). When vitamin D levels are sufficient, it ensures optimal absorption of these minerals, leading to the calcification and strengthening of the bone matrix. Additionally, vitamin D works with parathyroid hormone (PTH) to regulate calcium levels in the blood. If calcium levels decrease, vitamin D helps increase calcium absorption from the diet and signals the bones to release calcium into the bloodstream, maintaining the necessary balance for healthy bone metabolism (Laird et al., 2010). Vitamin D also influences bone remodeling by controlling

growth, differentiation, and mineralization. It also affects gene transcription and how osteoblasts respond, and the enzymes responsible for making and breaking down active vitamin D are functional in osteoblasts (Christodoulou et al., 2022). There are several stages involved in the process of bone remodeling, and vitamin D has a direct or indirect influence on the system. PTH and calcitriol are two hormones that play a crucial role in bone remodeling. This process is essential for maintaining the strength of bones and mineral balance in the body. The cycle of bone remodeling comprises of four primary stages. Initially, the cycle is activated by various stimuli, leading to the formation of mature osteoclasts from their precursors. These osteoclasts play a significant role in the resorption phase, where they attach to the bone surface, releasing enzymes and acids that dissolve bone minerals and degrade the matrix, creating small cavities. Following resorption, the cycle transitions to the reversal phase, marked by the cessation of osteoclast activity and the preparation of the site for new bone formation. This leads into the formation stage, where osteoblasts come into play, synthesizing new bone matrix that eventually mineralizes into new bone tissue. Osteoblasts that become embedded in the bone matrix evolve into osteocytes, cells that are integral to bone maintenance. The entire remodeling cycle is finely regulated by systemic hormones like parathyroid hormone and calcitriol, as well as local cytokines and growth factors. This ensures a delicate balance between bone destruction and formation to preserve bone integrity and support mineral homeostasis (Siddiqui & Partridge, 2016).

Cancer metastasis in the bones can severely disrupt the regular bone metabolism process. This process involves the creation and destruction of bone tissue by osteoblasts and osteoclasts, respectively, and requires a delicate balance. When cancer cells spread to the bone, they disturb this balance. For instance, prostate cancer cells that metastasize to bone can produce factors that

stimulate osteoblasts to form new bone. However, this new bone is usually structurally abnormal and weak (Goode et al., 2023). The abnormal activity of osteoclasts and osteoblasts in response to cancer cells can create an altered local environment that promotes the survival and proliferation of these malignant cells, further aggravating the disease's impact on the body. This pathological process is a significant factor contributing to the morbidity associated with bone metastases, including pain and reduced mobility. It can profoundly affect the quality of life of individuals affected by this condition (Ban et al., 2021).

When prostate cancer metastasizes to the bone it poses a significant challenge in patient management. The development of secondary bone tumors is linked to reduced patient survival and debilitating symptoms (Goode et al., 2023). Comprehension on how prostate tumors spread to the bones and cause bone metastases is crucial for better diagnosis and treatment of patients with advanced prostate cancer (Iglesias-Gato et al., 2023). Research has focused on studying the cellular and molecular structure of metastatic prostate tumors in the bone. The studies reveal that there are notable differences in protein and gene expression between the primary and metastatic tumors (Mehra et al., 2023). Below is an overview of the effect prostate cancer has on bone metabolism at each stage. Figure 2.2 provides an overview of how prostate cancer effects bone metabolism.

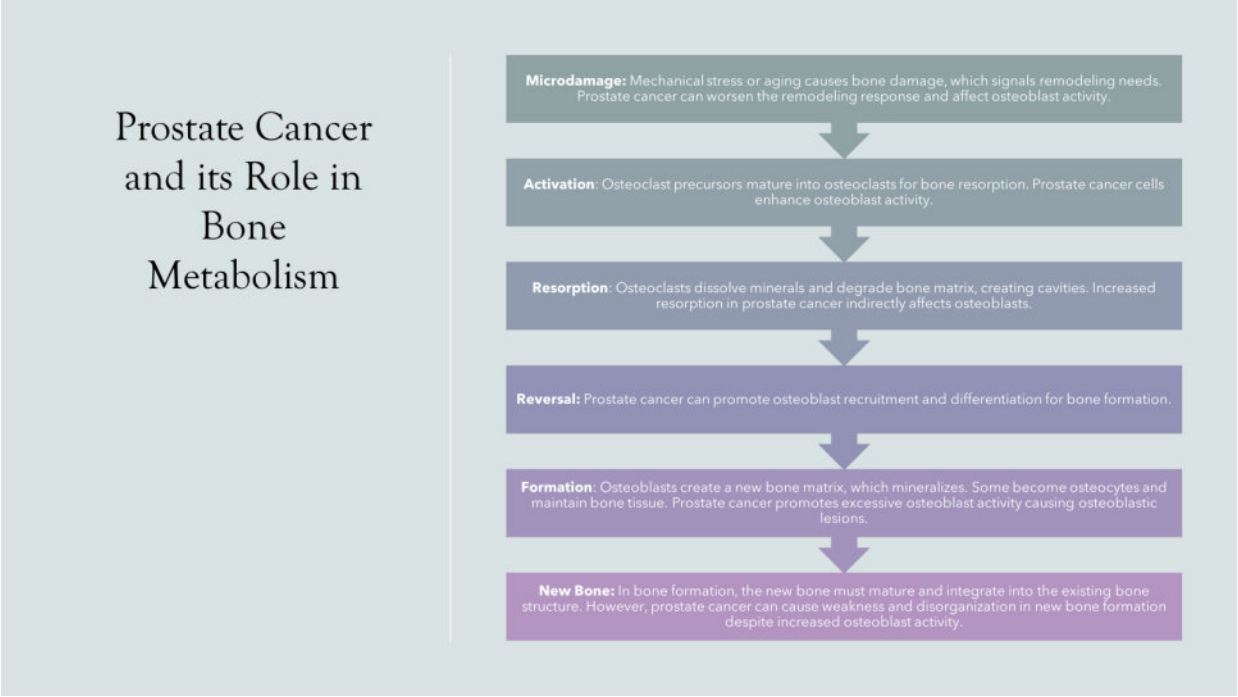

Figure 2.2 Prostate Cancer and its Role in Bone Metabolism.

(Lin et al., 2018; Siddiqui & Partridge, 2016)

The Importance of Research into Vitamin D and Nutritional Support for Prostate Cancer Patients.

Recent research indicates that Vitamin D levels can significantly affect prostate cancer outcomes. Considering the low risks associated with its supplementation and the large population that are at risk of inadequate Vitamin D levels, it is wise to expand our knowledge on this topic. Adequate Vitamin D levels can potentially inhibit cancer cell growth and reduce the risk of low BMD. Vitamin D supplementation can offer a cost-effective and straightforward strategy to improve patient quality of life and making it a vital area of exploration for healthcare providers. Nutritional research provides concrete evidence-based recommendations that healthcare professionals can use to guide their patients in making informed choices about their diet. this literature review serves as a good base of knowledge and underscores the potential for a holistic

approach to cancer care, emphasizing that optimal nutrition is a critical component of comprehensive treatment plans, with the potential to improve patient outcomes significantly.

CHAPTER III

METHODS

Aims and Objectives

The primary objective of this systematic review was to meticulously assess the intervention of vitamin D supplementation on prostate cancer positive patients of all stages and ages. The outcomes were measured by responses serum calcidiol related to survival rates, quality of life, overall survival, pain relief, and PSA response, muscular skeletal response, progression, prognosis, and Gleason score. To accomplish this, the objective this study employed a rigorous analysis of existing research, using the PRISMA Guidelines as a benchmark, to gain a deeper understanding of how vitamin D affects the clinical outcomes of this patient population (see figure 3.1).

Aims of this systematic review

- To evaluate the safety of vitamin D supplementation in prostate cancer-positive patients taking into account any adverse effects, treatment interactions, or contraindications.
- To investigate the effect of vitamin D supplementation on outcomes listed in the objectives (survival rates, quality of life, overall survival, pain relief, and PSA response, muscular skeletal response, progression, and Gleason score)
- Assess the possible correlation between osteomalacia development in prostate cancer patients and vitamin D supplementation.

- Analyze the effect of vitamin D supplementation on the overall survival rate of prostate cancer patients to identify significant correlations between vitamin D intake and long-term quality of life outcomes.

Through this systematic review, the aim was to gain a deeper understanding of the potential of vitamin D as a treatment option for prostate cancer patients.

Search

The search strategy targeted randomized controlled trials (RCTs) and intervention studies. The selection process involved screening for study characteristics (study design), participant demographics (prostate cancer patients receiving treatment), intervention details (vitamin D assessment methods, dosages), outcome measures (progression, prognosis, quality of life), and risk estimates (hazard ratios, odds ratios, relative risks) along with covariates adjusted for in the analysis. This comprehensive approach aimed to extract relevant data to enhance understanding of the relationship between vitamin D (25(OH)D) levels after supplementation and prostate cancer development, progression, quality of life, and treatment outcomes.

A systematic review of articles and information was obtained from the following search engines: Pubmed, MEDLINE, Scopus, and the Cochrane library. The following key words were utilized in each of the respective search engines.

PubMed/MEDLINE

("Vitamin D"[Mesh] OR "vitamin d*" OR "24,25-Dihydroxyvitamin D 3" OR "25-Hydroxyvitamin D 2") AND ("Prostatic Neoplasms"[Mesh] OR prostat*) AND ((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomized[tiab] OR randomised[tiab])

OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab])) NOT (animals[mh] NOT humans[mh])

Scopus

("vitamin d*" OR "24,25-Dihydroxyvitamin D 3" OR "25-Hydroxyvitamin D 2") AND prostat* AND (trial* OR random* OR rct* OR blind* OR placebo* OR "double-blind" OR "double blind" OR "single-blind" OR "single blind" OR "cross-over" OR crossover OR multicenter* OR control* OR factorial OR therap*) Limited to "article" and "prostate cancer"

("vitamin d*" OR "24,25-Dihydroxyvitamin D 3" OR "25-Hydroxyvitamin D 2") AND prostat* AND (trial* OR random* OR rct* OR blind* OR placebo* OR "double-blind" OR "double blind" OR "single-blind" OR "single blind" OR "cross-over" OR crossover OR multicenter* OR control* OR factorial OR therap*) AND (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (EXACTKEYWORD , "Prostate Cancer"))

Cochrane Library

("vitamin d*" OR "vitamin d2" OR "vitamin d 2" OR "vitamin d3" OR "vitamin d 3" OR "24,25-Dihydroxyvitamin D 3" OR "25-Hydroxyvitamin D 2") AND prostat*

We will also search for relevant grey literature and conference proceedings.

Study Selection and Eligibility Criteria

A comprehensive search strategy was implemented to systematically investigate the association between vitamin D serum 25(OH)D levels after supplementation and prostate cancer progression, prognosis, and quality of life. The eligibility criteria involved studies with prostate cancer patients of all stages and ages, focusing on measuring blood serum vitamin D serum 25(OH)D levels following oral supplementation. Due to the varied treatment options and staging

of prostate cancer the research studies were narrowed to randomized controlled trials and intervention studies. The comparison groups included healthy individuals without prostate cancer, different stages of prostate cancer (early-stage vs. advanced-stage), and various treatment approaches (e.g., surgery, radiation, hormone therapy, physical exercise). The search was conducted on reputable databases such as PubMed, Scopus, and Cochrane, utilizing a combination of Medical Subject Headings (MeSH) terms and keywords tailored for each database.

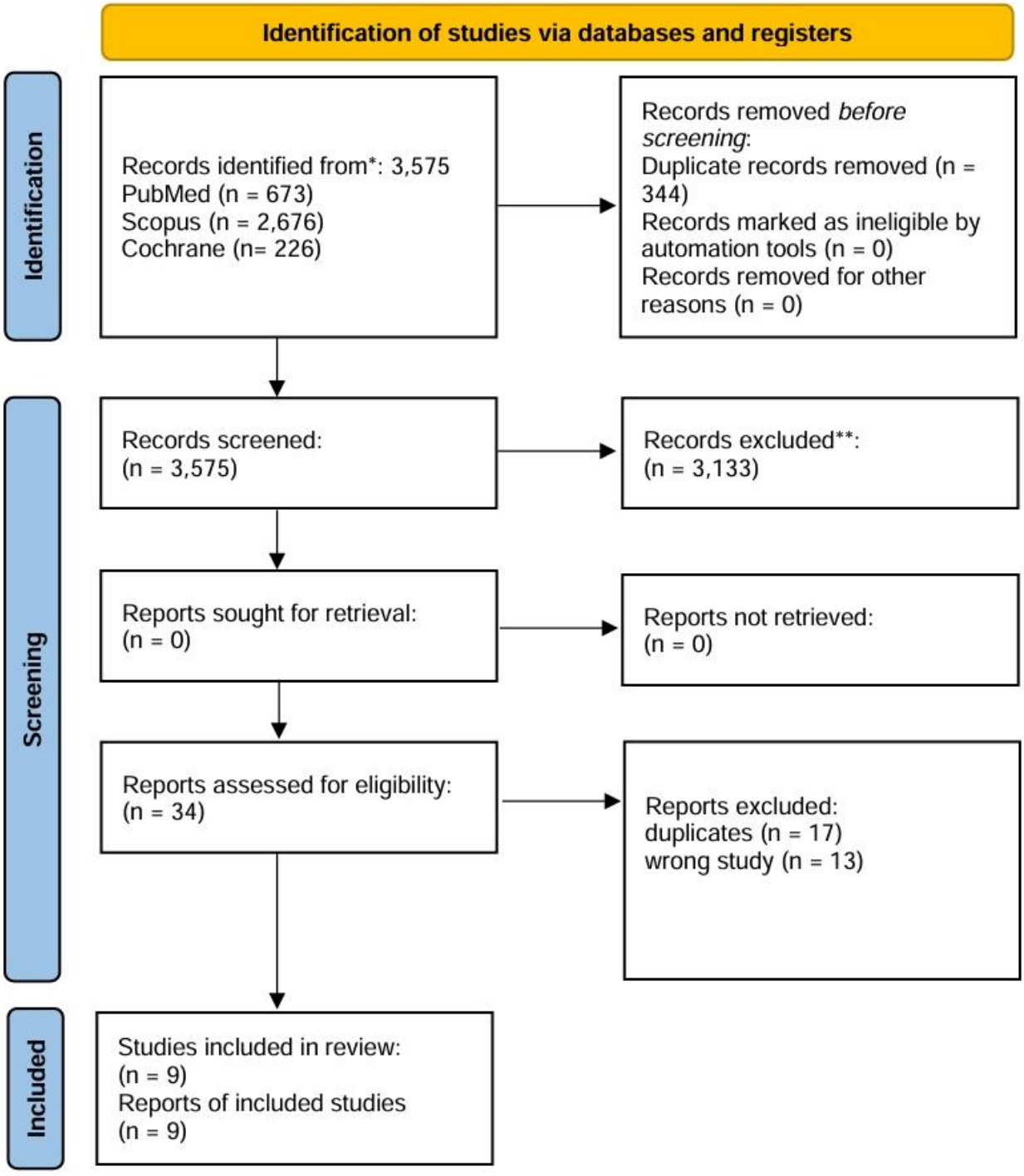

Figure 3.1 PRISMA flow chart

PRISMA FLOWCHART (Page et al., 2021)

CHAPTER IV

RESULTS

Data abstraction and quality assessment

During the data extraction process of nine studies, various characteristics were meticulously recorded. Each study, identified by its author and year of publication, presented unique designs, from randomized controlled trials to observational analyses. The noted participant demographics, with varying sample sizes, encompass a broad age range and diverse ethnic backgrounds. The primary interventions in these studies were centered on vitamin D, and assessment methods included serum level measurements calcidiol and different supplementation dosages. Outcome measures were focused on prostate cancer by measured by responses in serum calcidiol, survival rates, quality of life, overall survival, pain relief, and PSA response, muscular skeletal response, progression, and Gleason score. The extracted risk estimates, such as hazard ratios, odds ratios, and relative risks, were used to quantify the relationship between vitamin D supplementation and prostate cancer outcomes. Additionally, the analysis considered various covariates to ensure a thorough understanding of the effects of vitamin D. To ensure a comprehensive and reliable synthesis of the collected data, each study was scrutinized using appropriate tools relevant to its design. This assessment involved evaluating the risk of bias and identifying methodological strengths and weaknesses. Table 4.1 provides an overview of each study's: authorship, study design, year of publication, sample size, length of study, intervention, and outcome.

Table 4.1 Study Summaries

Author(s); Year	Study Design	Sample Size	Length of Study	Intervention	Outcome
Dalla Via et al., 2021	Randomized Controlled Trial	70 patients	12 months	The study evaluated the impact of exercise and a multinutrient supplement, including vitamin D, on musculoskeletal health, using serum 25(OH)D levels for assessment.	The intervention did not show significant effects on bone or body composition outcomes, but it did improve leg muscle strength (14.5%) and dynamic mobility (−9.3%) compared to controls, suggesting positive effects on musculoskeletal health.
Jarrard et al., 2016	Randomized Placebo-Controlled Trial	15 patients	31 months	The study compares the effects of placebo and cholecalciferol/genistein on measuring calcitriol 1,25(OH)2D in prostate tissue.	No significant difference was found in prostate tissue calcitriol levels between the two groups. Although a slight increase in serum calcitriol was observed in the vitamin D and genistein group, there were no significant effects on serum calcidiol.

Table 4.1 (continued)

Author(s); Year	Study Design	Sample Size	Length of Study	Intervention	Outcome
Wagner et al., 2013	Double Blinded Randomized Controlled Trial	66 patients	46 months	The study aimed to determine the serum and prostate tissue levels of vitamin D metabolites in patients following oral vitamin D3 administration.	Higher doses of vitamin D3 have a positive impact on prostatic vitamin D metabolite levels, potentially influencing cellular proliferation. The study suggests an inverse association between the calcitriol level attained in the prostate and Ki67 intensity, emphasizing potential anti-proliferative effects.

Table 4.1 (continued)

Author(s); Year	Study Design	Sample Size	Length of Study	Intervention	Outcome
Marshall et al., 2012	Open-Label Clinical Trial	52 patients	45 months	PSA serum levels were monitored at entry, every two months for a year, and biopsy procedures were performed a year, and biopsy procedures were performed before enrollment and after a year of supplementation.	Vitamin D3 supplementation showed no adverse events and potential positive impact in reducing positive cores for low-risk prostate cancer. However, treatment response showed heterogeneity with 34% of subjects experiencing an increase in positive cores or Gleason score.
Campbell et al., 2021	Clinical Trial	68 patients	77 months	PSA was monitored at 4-month intervals, while serum vitamin D 25(OH)D levels were measured at the initial visit, 6 weeks post-initiation, and again at 4-month intervals.	The reporting of results highlighted a potential association between higher vitamin D levels and a downward PSA trend, indicating a potential protective effect in the context of active surveillance for prostate cancer.

Table 4.1 (continued)

Author(s); Year	Study Design	Sample Size	Length of Study	Intervention	Outcome
Cooper et al., 2021	Double-Blinded, Parallel, Placebo-Controlled, Randomized Trial	103 patients	24 months	D3 6000 IU significantly increased 25(OH)D levels during treatment, with similar PSA slopes for patients receiving D3 or placebo, regardless of treatment order or study season.	The PSA slope was similar between patients receiving D3 or placebo, irrespective of the order of D3 and placebo or the study season.
Khriguian et al., 2021	Phase III Randomized Trial	329 patients	28 months	The clinical bone density status, including normal, osteopenia, and osteoporosis, was monitored.	The results indicated a mean percent change in bone mineral density of -2.65%, -2.76%, and -4.27% for these respective sites, with an average decrease in bone mineral density across all sites of -3.2%.

Table 4.1(continued)

Author(s); Year	Study Design	Sample Size	Length of Study	Intervention	Outcome
Al-Hussaini et al., 2011	Phase II Randomized Trial	120 patients	6 months	The 25(OH)D plasma levels, serum and urine calcium levels, parathyroid hormone (PTH) plasma levels and signs of toxicity were assessed.	The study reported that 25(OH)D3 levels achieved were proportional to the vitamin D3 dose, and there were no changes in parathyroid hormone (PTH) levels related to vitamin D3 dose, serum level of 25(OH)D3, or duration of supplementation.
Peppone et al., 2017	Phase II Randomized Trial	69 patients	24 weeks	BMD was assessed at the total hip (TH) and lumbar spine (LS) via DXA at pre- and post-intervention. ANCOVA was used to test the change in BMD between groups.	The study reported a significant reduction in bone loss for the high-dose vitamin D group compared to the recommended vitamin D group, specifically for total hip bone mineral density (BMD%).

Risk of Bias

The studies reviewed use various research methodologies such as randomized controlled trials (RCTs), open-label clinical trials, and phase II and III trials. These studies were conducted in different global locations and targeted different populations. The focus of these investigations

was on the effects of vitamin D supplementation on survival rates, quality of life, overall survival, pain relief, and PSA response, muscular skeletal response, progression, prognosis, and Gleason score in male cohorts who had prostate cancer and were at risk of vitamin D deficiency. Several studies have found ways to reduce the risk of selection bias through randomization techniques. Randomized controlled trials (RCTs) by Dalla Via et al., Wagner et al., and Cooper et al. have bolstered the internal validity of their outcomes. However, the potential for selection bias is higher in open-label studies with limited participants such as the one by Marshall et al. and Jarrard et al. This could impact the universality of their findings. Wagner et al. and Cooper et al. utilized double-blinded designs to reduce performance and detection biases by concealing the intervention allocations from both participants and researchers. However, the open-label nature of Marshall et al.'s study and the unspecified blinding status in others could lead to biases in intervention administration and outcome evaluation.

Studies with high completion rates, such as those conducted by Dalla Via et al. and Wagner et al., exhibit low levels of attrition bias. However, the risk of such bias still exists in cases where there is partial outcome data or limited follow-up information. Studies like Dalla Via et al. and Campbell et al., which document intervention effects, adherence, and adverse reactions in detail, indicate efforts to minimize reporting bias. However, the possibility of selective reporting cannot be ruled out, particularly in cases where trial protocols or predetermined analysis strategies are not referenced.

Acknowledgment of funding sources and potential conflicts of interest, as seen in the study by Dalla Via et al., is vital for evaluating biases linked to study sponsorship. The mixed responses to vitamin D supplementation underscore the necessity of considering individual

baseline characteristics, adherence levels, and the potential interplay between various interventions, such as exercise and multinutrient supplements, in interpreting study outcomes. The studies that have been discussed provide valuable information about the role of vitamin D in musculoskeletal health, prostate cancer, and bone health. However, it's important to note that biases can exist and impact the results of these studies. Factors such as the study design, the number of participants, blinding procedures, and reporting practices can significantly influence these biases.

Table 4.2 Risk of Bias

Study Aspect	Description
Study Diversity	Studies vary in design (RCTs, open-label, phase II/III trials), location, and population, focusing on vitamin D's effects on musculoskeletal health, prostate cancer progression, and bone mineral density.
Selection Bias	Mitigated in RCTs through randomization (Dalla Via et al., Wagner et al., Cooper et al.). Open-label studies and those with small sample sizes (e.g., Jarrard et al.) present higher risks, impacting generalizability.
Performance and Detection Bias	Minimized in double-blinded trials (Wagner et al., Cooper et al.). Open-label studies (Marshall et al.) and those without specified blinding procedures potentially introduce these biases.
Attrition Bias	Lower in studies with high completion rates (Dalla Via et al., Wagner et al.). The risk persists with incomplete outcome data or inadequate follow-up.
Report Bias	Efforts towards transparency in reporting intervention effects, adherence, and adverse effects (Dalla Via et al., Campbell et al.) reduce this risk. The potential for selective outcome reporting remains.
Other Biases	The acknowledgment of funding sources and conflicts of interest (e.g., Dalla Via et al.) is crucial for assessing biases related to study sponsorship. Diverse responses to vitamin D supplementation highlight the importance of considering baseline characteristics and the interplay between interventions.
Future Research Directions	It is crucial to follow strict study designs, report detailed methodologies, and adhere to protocol-specified outcomes to improve the quality of evidence.

Studies Summaries

Musculoskeletal Responses to Exercise Plus Nutrition in Men with Prostate Cancer on Androgen Deprivation: A 12-Month RCT

This study was systematically screened per protocol. In terms of the study selection process, it employed a randomized controlled trial (RCT) design involving sixty men with prostate cancer on androgen deprivation therapy, with 86% completing the 12-month study. The study characteristics revealed a mean exercise adherence of 56% and supplement adherence of 77%, which emphasized participant engagement. The researchers did not disclose a bias in the article; however, funding was disclosed with the main sponsor being Deakin University, and charities, societies, and foundations were declared secondary sponsors. The results of the individual study indicated no significant effects of the intervention on bone or body composition outcomes. However, noteworthy improvements were observed in leg muscle strength (14.5%) and dynamic mobility (−9.3%) compared to controls, suggesting a positive impact on musculoskeletal health. Per-protocol analysis of outcomes in the study design demonstrated the preservation of femoral neck areal bone mineral density and improved total body lean mass relative to controls.

Of the 214 men who showed interest, 70 were chosen for the study. These men were generally older, with an average age of 71, and a significant number were either overweight or obese. A prevalent presence of comorbidities among the participants indicated a complex health profile, common in older adults with cancer. The men had been living with a prostate cancer diagnosis for over three years on average, and most had been receiving ADT for about a year.

This study design was structured to evaluate the effects of an intervention group (exercise and supplementation) that engages in a combined regimen of exercise and a multinutrient supplement, including vitamin D. This intervention design was significant as ADT is known to

have side effects that can impact musculoskeletal health, such as muscle weakness and bone density loss. The adherence to the exercise regimen was moderate, at 56%, but adherence to the nutritional supplement was notably higher, at 77%. This difference in adherence rates could be due to the varying demands of maintaining a regular exercise schedule compared to taking a supplement. The study finds that, initially, a fair proportion of participants, about 17%, had insufficient levels of vitamin D. This is a crucial finding as vitamin D plays a significant role in bone health, and its deficiency can exacerbate the musculoskeletal issues associated with ADT. After 6 months, there is a significant improvement in serum 25(OH)D levels in the exercise and supplementation group, although this improvement is not sustained over the full 12 months. This suggests that while vitamin D supplementation can effectively increase levels in the short term, maintaining these levels might require ongoing intervention.

The benefits of the exercise and nutrition regimen extend beyond just vitamin D levels. The intervention leads to improvements in leg muscle strength and dynamic mobility, which are critical for the overall quality of life and functional independence of these patients. The preservation of femoral neck areal bone mineral density and an improvement in total body lean mass in participants adhering strictly to the protocol are particularly noteworthy. These results suggest that targeted exercise and nutrition can help mitigate some of the musculoskeletal side effects of ADT.

In terms of safety and tolerability, the study reported no serious adverse events related to the intervention. The most common issue was minor musculoskeletal complaints, highlighting the need for careful monitoring and potentially modified exercise programs for some individuals. The cessation of supplement intake by a few participants due to gastrointestinal issues also underscores the importance of considering individual tolerability to interventions.

Furthermore, the study lists various factors that could influence the results, such as the duration of ADT and changes in prostate cancer treatment, including the commencement of radiation therapy or chemotherapy. The lack of significant alterations in the results, despite these factors, strengthens the study's findings. The study underscores the potential of a combined exercise and nutritional supplement regimen, particularly including vitamin D, in enhancing musculoskeletal health in men undergoing ADT for prostate cancer. While the regimen shows promise in the short-term improvement of vitamin D levels and physical functioning, the long-term sustainability, and benefits of such an intervention are areas for further research. Table 4.2 provides an overview of the study.

Table 4.3 Musculoskeletal Responses to Exercise Plus Nutrition in Men with Prostate Cancer on Androgen Deprivation: A 12-Month RCT

Aspect	Details
Study Completion Rate	60 men (86%) completed
Exercise Adherence (%)	56
Supplement Adherence (%)	77
Effects on Bone/Body Composition	No effects
Leg Muscle Strength Improvement (%)	14.5% (95% CI, -0.2 to 29.2); P = 0.007
Dynamic Mobility Improvement (%)	-9.3% (95% CI, -17.3 to -1.3); P = 0.014
Femoral Neck BMD Preservation (%)	1.9% (95% CI, 0.1 to 3.8); P = 0.026
Total Body Lean Mass Improvement (kg)	1.0 kg (95% CI, -0.23 to 2.22); P = 0.044
Baseline Serum 25(OH)D nmol/L	69.8, 12 men (17%) insufficient (<50)
Increase in Serum 25(OH)D after 6 months nmol/L	12.4 nmol/L (95% CI, 8.9 to 19.9); P = 0.001
Significant Changes in Serum IGF-1, CRP, or PSA	No significant effects or changes after 6 or 12 months

Phase I , Randomized Placebo-Controlled Trial Of Single High Dose Cholecalciferol (Vitamin D3) And Daily Genistein (G-2535) Versus Double Placebo In Men With Early-Stage Prostate Cancer Undergoing Prostatectomy.

The study underwent a systematic screening per protocol. The study selection process involved a randomized placebo-controlled trial design, enrolling a total of 15 patients, with 8 in the placebo arm and 7 in the vitamin D and genistein arm. All patients completed the study, with some missed doses in both groups and adverse events reported in 4 patients in the placebo group and 5 in the vitamin D and genistein group. The study characteristics outlined the administration of a single high dose of cholecalciferol and daily genistein in the intervention group, compared to a double placebo in the control group, within the context of early-stage prostate cancer patients undergoing prostatectomy. The reported results indicated that prostate tissue calcitriol levels did not significantly differ between the two groups. While a trend toward increased serum calcitriol was observed in the vitamin D and genistein group, no significant effects were observed on serum calcidiol. The study's limitations, potential reporting biases, and the overall certainty of evidence require further exploration for a comprehensive understanding of its implications in early-stage prostate cancer and vitamin D plus genistein interventions.

For the design of the clinical trial subjects were randomly divided into two groups. The first group received a one-time dose of 200,000 IU of cholecalciferol orally on the first day, alongside a daily dose of 600 mg of genistein. The second group was given a placebo equivalent for both cholecalciferol and genistein for a period of 21-28 days leading up to their radical prostatectomy surgery. A total of fifteen patients participated in the study, with eight assigned to the placebo group and seven to the vitamin D and genistein (VD + G) group. All participants successfully completed the study, although there were instances of missed doses, with one case in the placebo group (12%) and two cases in the VD + G group (28%). Adverse events were

reported in four patients from the placebo group and five from the VD + G group, including one severe case of hypophosphatemia in the placebo group that was possibly linked to the study medication. The study also involved comprehensive testing, including serum and tissue biomarkers and chemistries to assess the impact of the treatments.

The primary endpoint of the study, the level of calcitriol in prostate tissue, did not show a significant difference between the two groups, with a p-value of 0.92. Detectable tissue calcitriol was found in only one patient each from the VD + G and placebo groups. However, there was a notable, though not statistically significant, increase in serum calcitriol levels in the VD + G group compared to the placebo. No significant changes were observed in serum calcidiol levels, the standard measure of vitamin D status, or in serum T4 levels. There was a trend towards a decrease in serum TSH in the VD + G group, but no significant difference between the groups was found. The study also included immunostaining for various tissue biomarkers and utilized Vectra™ automated quantitative analysis to focus on the epithelial component of the prostate tissue, which showed a trend towards increased TUNEL staining in the VD + G group, indicating a potential increase in apoptosis within prostate cancer tissue samples.

This study highlighted a trend towards increased serum calcitriol levels in patients receiving the combination of cholecalciferol and genistein, although no significant increase was observed in tissue levels. The study also observed an increase in apoptosis and AR (androgen receptor) expression in the prostate cancer samples from the VD + G group, suggesting potential bioactivity of the combination treatment. However, due to the small sample size and the multiple comparisons made, firm conclusions could not be drawn. The lack of significant change in calcidiol levels also suggests that the administered dose of cholecalciferol might not have been

sufficient to test the hypothesis that genistein would enhance its effect at the tissue level (Jarrard et al., 2016). Table 4.3 provides an overview of the study.

Table 4.4 Phase I , Randomized Placebo-Controlled Trial Of Single High Dose Cholecalciferol (Vitamin D3) And Daily Genistein (G-2535) Versus Double Placebo In Men With Early-Stage Prostate Cancer Undergoing Prostatectomy. - Outcome

Aspect	Details
Number of Patients Enrolled	15 (Placebo: 8, VD + G: 7)
Treatment Groups	(1) Placebo, (2) Vitamin D + Genistein
Compliance and Study Completion	All patients were compliant and completed the study
Missed Doses (Placebo / VD + G)	Placebo: 1 (12%), VD + G: 2 (28%)
Adverse Events (Placebo / VD + G)	Placebo: 4, VD + G: 5
Severe Hypophosphatemia in Placebo Arm	1 case, possibly related to study drug
Primary Endpoint: Prostate Tissue Calcitriol Levels	No significant difference (p=0.92)
Serum Calcitriol Trend	Increased trend (p=0.08)
Effect on Serum Calcidiol	No significant effect (p=0.5)
Trend in Serum TSH Levels	Decreasing trend in VD + G (p=0.055)
Effect on Serum T4	Not altered
Tissue Biomarker Analysis	Performed, including apoptosis markers
TUNEL Staining in Prostate Cancer Tissue	Greater in VD + G (p=0.16)
AR Expression in Prostate Cancer Tissue	Greater in VD + G relative to placebo in cancer samples (p=0.041), not in benign (p=0.4)

Randomized Clinical Trial of Vitamin D3 Doses on Prostatic Vitamin D Metabolite Levels and Ki67 Labeling in Prostate Cancer Patients

The study conducted a systematic screening according to the protocol, employing a randomized clinical trial design to explore the effects of various doses of vitamin D3 on prostatic vitamin D metabolite levels and Ki67 labeling in prostate cancer patients. Results indicated a dose-dependent increase in prostate tissue and serum levels of vitamin D metabolites,

particularly calcitriol, with significantly higher concentrations observed in the 40,000-IU/d group compared to other dose groups. However, Ki67 measures did not differ greatly among the vitamin D dose groups. Nonetheless, the cross-sectional analysis suggested an inverse relationship between the calcitriol level achieved in the prostate and Ki67 intensity, indicating potential anti-proliferative effects. The study findings underscored the positive impact of higher doses of vitamin D3 on prostatic vitamin D metabolite levels, potentially influencing cellular proliferation dynamics.

Regarding vitamin D metabolite analyses, serum levels of 25(OH)D3 and 24,25(OH)2D3 significantly increased across all three vitamin D3-treated groups in a dose-response manner, with the highest levels observed in the 40,000-IU/d group. Serum calcitriol levels also rose considerably with dosing, with the highest concentration achieved in the highest dose group. Prostate tissue levels of various vitamin D metabolites increased dose-dependently, with significantly higher concentrations observed in the 40,000-IU/d group than in other doses. Serum levels of vitamin D metabolites were strongly correlated with their mean levels in prostate tissue. Moreover, there was no significant relationship between circulating or prostatic concentrations of vitamin D metabolites and the duration of vitamin D dosing.

The clinical trial data support the hypothesis that high oral vitamin D dosing can modulate prostatic in vivo vitamin D metabolism. The observed decrease in Ki67 labeling and modest declines in serum PSA and PTH with higher prostate calcitriol levels achieved through vitamin D doses suggest a potential clinical benefit. Notably, the vitamin D doses administered were well tolerated by prostate cancer patients without signs of toxicity.

Safety measures did not deteriorate with dosing, and combined, higher-dose groups exhibited lower serum PTH and PSA than those at the end of the study (Wagner et al., 2013). Table 4.4 provides an overview of the study.

Table 4.5 Randomized Clinical Trial of Vitamin D3 Doses on Prostatic Vitamin D Metabolite Levels and Ki67 Labeling in Prostate Cancer Patients

Aspect	Details
Dose-Dependent Increase in Vitamin D Metabolites	Increased dose-dependently ($P < .03$)
Highest Levels in 40,000 IU/d Group	Significantly higher than in other dose groups ($P < .03$)
Correlation Between Prostate and Serum Vitamin D Levels	Positive correlation ($P < .0001$)
Ki67 Measures Among Vitamin D Dose Groups	No significant difference
Association of Prostate Calcitriol with Ki67 Intensity	Inverse association ($P < .05$)
Safety Measures	Did not change adversely with dosing
Serum PTH and PSA in Higher-Dose Groups Compared to 400 IU/d	Lower in higher-dose groups ($P < .02$)
Clinical Trial Conclusion	Supports hypothesis of modulatable prostatic vitamin D metabolism by high dosing
Tolerance of Vitamin D Doses in Prostate Cancer Patients	Well tolerated without signs of toxicity

Vitamin D3 Supplementation at 4000 International Units Per Day for One Year Results in a Decrease of Positive Cores at Repeat Biopsy in Subjects with Low-Risk Prostate Cancer under Active Surveillance

The study was systematically screened per protocol. The study selection process involved a supplementation trial with 44 subjects under active surveillance for low-risk prostate cancer, investigating the effects of vitamin D3 at 4000 IU per day for one year. The study characteristics outlined no adverse events associated with vitamin D3 supplementation. While no significant changes in PSA levels were observed, 55% of subjects showed a decrease in the number of positive cores or Gleason score. However, 34% of subjects experienced an increase in positive

cores or Gleason score, emphasizing potential heterogeneity in the treatment response. The reporting of results highlighted a potential positive impact of vitamin D3 supplementation in reducing positive cores at repeat biopsy, indicative of a favorable response in subjects under active surveillance for low-risk prostate cancer. Further synthesis and exploration of the study's implications and design would give a better overall certainty of evidence of low-risk prostate cancer and vitamin D supplementation (Marshall et al., 2012). Table 4.5 provides an overview of the study.

Table 4.6 Vitamin D3 Supplementation at 4000 International Units Per Day for One Year Results in a Decrease of Positive Cores at Repeat Biopsy in Subjects with Low-Risk Prostate Cancer under Active Surveillance

Aspect	Details
Recommended Vitamin D3 Supplementation	4000 IU/d
Adverse Events Associated with Vitamin D3 Supplementation	None observed
Changes in PSA Levels	No significant changes
Subjects with Decrease in Positive Cores or Gleason Score	24 of 44 subjects (55%)
Subjects with No Change	5 subjects (11%)
Subjects with Increase in Positive Cores or Gleason Score	15 subjects (34%)

Correlative Analysis of Vitamin D and Omega-3 Fatty Acid Intake in Men on Active Surveillance for Prostate Cancer

This study underwent systematic screening per protocol. The study examined the effects of vitamin D and omega-3 fatty acid supplementation on prostate-specific antigen (PSA) levels in men who were undergoing active surveillance for prostate cancer. The study was based on a randomized controlled trial (RCT) and provided a thorough analysis. The trial focused on the correlation between these supplements and PSA levels. It involved 68 male participants with an average age of 63. Initial measurements revealed that these men had an average PSA level of

5.11 ng/mL and vitamin D levels at 36.9 ng/mL, which is on the lower end of the normal range, highlighting an area for potential intervention.

The researchers tracked the progression of PSA levels throughout the study, establishing a mean monthly increase of 0.11 ng/mL. This tracking helped identify trends and patterns in PSA levels among the participants. Vitamin D levels were closely monitored, with the study noting a significant mean increase of 4.65 ng/mL per month in these levels, reflecting the direct impact of vitamin D supplementation on serum concentrations over time.

A crucial finding was that individuals with higher initial vitamin D levels were twice as likely to experience a reduction in PSA levels. This observation was quantified by an odds ratio of 2.04, with a statistically significant p-value of 0.039, suggesting a potentially protective role of vitamin D against prostate cancer progression. The study also examined the safety and tolerability of nutritional intervention. At the same time, most participants responded well; a few experienced loose bowel movements, necessitating adjustments in omega-3 and curcumin dosages. This highlighted the importance of personalized management to enhance patient adherence and mitigate adverse effects. An in-depth examination of dietary intake and supplementation effects revealed notable stability or positive changes in omega-3 and omega-6 levels, indicating strong adherence to the nutritional regimen. These findings are significant as they suggest that consistent supplementation and dietary adjustments can lead to beneficial changes in fatty acid profiles, which might influence cancer progression and general health.

Moreover, the study's follow-up procedures, including biopsies in 55 patients, did not indicate any pathological or clinical disease progression, further substantiating the intervention's potential efficacy.

This aspect of the research underscores the importance of continuous monitoring and the potential of nutritional interventions in managing prostate cancer effectively. The study's results provide valuable insights into the complex interplay between vitamin D supplementation, omega-3 fatty acid intake, and PSA level dynamics in men under active surveillance for prostate cancer. The findings suggest that higher initial vitamin D levels may offer protective benefits, potentially influencing the management and outcome of prostate cancer (Khriguian et al., 2021). Table 4.6 provides an overview of the study.

Table 4.7 Correlative Analysis of Vitamin D and Omega-3 Fatty Acid Intake in Men on Active Surveillance for Prostate Cancer

Aspect	Details
Intervention	Vitamin D and Omega-3 PUFA supplementation
PSA Slope Mean and 95% CI (ng/mL/month)	0.11 (0-0.25)
Vitamin D Serum Levels Slope Mean and 95% CI (ng/mL/month)	4.65 (3.09-5.98)
Effect of Initial Vitamin D Levels on PSA Trend	Higher initial levels associated with downward trend (OR = 2.04, 95% CI 1.04-4.01, P = .04)
Follow-up Biopsy Results	55 patients showed no progression of disease
Adverse Events	3 patients had loose bowel movements requiring dose adjustments

Randomized Placebo-Controlled, Double-Blind Study of Vitamin D3 Replacement in Men on Active Surveillance for Prostate Cancer

This study underwent systematic screening per protocol. In the study selection process, the randomized, placebo-controlled, double-blind design was used, focusing on vitamin D3 replacement in men under active surveillance for prostate cancer. The study indicated no difference between the overall recruited and evaluable patients in age, Gleason grade, T stage, or PSA or D3 levels. However, the recruited and evaluable samples differed by race, and the study observed that D3 supplementation at 6000 IU increased 25(OH)D3 levels during the on-

treatment period. The PSA slope was similar between patients receiving D3 or placebo, irrespective of the order of D3 and placebo or the study season. Notably, the PSA slope was significantly higher for Gleason grade 2 patients than for Gleason grade 1 patients. The risk of bias in the study was not explicitly addressed, necessitating a more detailed evaluation of the methodology to assess potential sources of bias. The reporting of results indicated a potential impact of D3 supplementation on 25(OH)D3 levels but raised questions about the observed differences in PSA slope between Gleason grades, warranting further exploration (Cooper et al., 2021). Table 4.7 provides an overview of the study.

Table 4.8 Randomized Placebo-Controlled, Double-Blind Study of Vitamin D3 Replacement in Men on Active Surveillance for Prostate Cancer

Aspect	Details
6000 IU D3 Daily Replacement Effect	Safe and increased 25(OH)D3 levels but no effect on PSA levels or slope
Differences Between Recruited and Evaluable Patients	Differed by race (p=0.03); 5 of 10 African Americans exited the study
Impact on 25(OH)D3 Levels	Increased during on-treatment period (p<0.001)
PSA Slope Comparison (D3 vs. Placebo)	Similar for patients receiving D3 or placebo
PSA Slope Difference by Gleason Grade (GG)	5-fold higher for GG2 than GG1 (GG2: 0.001013 ± SE 0.000145 vs. GG1: 0.000145 ± SE 0.000077; p<0.001)
Treatment-Related Adverse Events (AEs)	5 occurred, including 1 grade 3 (hypophosphatemia); no grade 4 or 5 AEs

The Clinical Significance of Bone Mineral Density Changes Following Long-Term Androgen Deprivation Therapy in Localized Prostate Cancer Patients

The study underwent systematic screening per protocol. In the study selection process, the focus was on assessing the clinical significance of bone mineral density changes associated with long-term androgen deprivation therapy in localized prostate cancer patients. The study characteristics involved the measurement of the lumbar spine, femoral neck, and total femoral bone mineral density for many patients. The results indicated a mean percent change in bone

mineral density of -2.65%, -2.76%, and -4.27% for these respective sites, with an average decrease in bone mineral density across all sites of -3.2%. Notably, most patients (83%) did not experience a decline in bone mineral density category. However, eight patients (4%) became osteoporotic. Reporting of results focused on the magnitude and pattern of bone mineral density changes associated with androgen deprivation therapy, suggesting potential clinical implications for bone health in localized prostate cancer patients (Khriguian et al., 2021). Table 4.8 provides an overview of the study.

Table 4.9 The Clinical Significance of Bone Mineral Density Changes Following Long-Term Androgen Deprivation Therapy in Localized Prostate Cancer Patients

Aspect	Details
Purpose of Study	To quantify changes in BMD in men with high-risk prostate cancer on long-term androgen deprivation therapy and calcium and vitamin D supplementation.
Materials and Methods	Patients in PCS-V trial received 28 months of luteinizing hormone-releasing hormone agonist and calcium and vitamin D supplementation (500 mg calcium BID + 400 IU vitamin D3 BID). Areal density and T-scores at baseline and 30 months follow-up were analyzed.
Bone Mineral Density Analysis Sites	Lumbar Spine, Femoral Neck, Total Femoral
Mean Percent Change in BMD (Lumbar Spine, Femoral Neck, Total Femoral)	Lumbar Spine: -2.65%, Femoral Neck: -2.76%, Total Femoral: -4.27% ($p < 0.001$ for all)
Average Decrease in BMD Across All Sites	-3.2%
Patients with No Decline in BMD Category	83% of patients
Patients Who Became Osteoporotic	8 patients (4%)
Study Conclusions	Calcium and vitamin D supplementation may suffice for most patients on long-term androgen deprivation therapy, despite a mild decline in BMD.

Serum 25(OH) vitamin D3 response to vitamin D3 supplementation in men with prostate cancer: Results of a randomized phase II trial

The study underwent a thorough screening per protocol. The study selection process focused on investigating the serum 25(OH) vitamin D3 response to vitamin D3 supplementation in men with prostate cancer. The study characteristics included a randomized phase II trial design with a specific emphasis on assessing the impact of vitamin D3 supplementation on serum 25(OH) vitamin D3 levels. Results from the individual study highlighted that toxicity and adverse events related to vitamin D3 were negligible, with no clinically significant changes in serum or 24-hour urine calcium observed. The study reported that 25(OH)D3 levels achieved were proportional to the vitamin D3 dose, and there were no changes in parathyroid hormone (PTH) levels related to vitamin D3 dose, serum level of 25(OH)D3, or duration of supplementation. The study provides valuable insights into the serum response to vitamin D3 supplementation in men with prostate cancer (Al-Hussaini et al., 2011). Table 4.9 provides an overview of the study.

Table 4.10 Serum 25(OH) vitamin D3 response to vitamin D3 supplementation in men with prostate cancer: Results of a randomized phase II trial

Aspect	Details
Tolerance of VD3 Supplementation	All 4 doses well tolerated
Achievement of Normal 25D3 Serum Concentrations at 3 Months	>80% of patients achieved normal concentrations
Safety and Appropriateness for Future Study	4,000 IU or 6,000 IU daily doses are very safe and appropriate
Toxicity and Adverse Events	Negligible, not clearly related to VD3
Changes in Serum or 24hr Urine Calcium	No clinically significant changes
25D3 Levels Proportionality to VD3 Dose	Proportional to VD3 dose
Changes in PTH Level	No changes related to VD3 dose, serum level of 25D3, or duration of supplementation

A Phase II RCT Of High-Dose Vitamin D Supplementation for Androgen Deprivation Therapy (ADT)-Induced Bone Loss Among Older Prostate Cancer (Pca) Patients

The study was subjected to a comprehensive screening per protocol. In the study selection process, the focus was on examining the effects of high-dose vitamin D supplementation on androgen deprivation therapy-induced bone loss in older prostate cancer patients. The study characteristics revealed a randomized controlled trial (RCT) design targeting a population of prostate cancer patients undergoing androgen deprivation therapy. Results from the individual study indicated that 59 prostate cancer patients were accrued, with serum analyses confirming high compliance in both high-dose and recommended vitamin D groups. The study reported a significant reduction in bone loss for the high-dose vitamin D group compared to the recommended vitamin D group, specifically for total hip bone mineral density (BMD%). Overall the study provides valuable insights into the potential benefits of high-dose vitamin D supplementation in mitigating ADT-induced bone loss (Peppone et al., 2017). Table 4.10 provides an overview of the study.

Table 4.11 A Phase II RCT Of High-Dose Vitamin D Supplementation for Androgen Deprivation Therapy (ADT)-Induced Bone Loss Among Older Prostate Cancer (Pca) Patients

Aspect	High-dose VITD (hVITD)	Recommended Vitamin D (rVITD)
Study Aim	To evaluate the effect of high-dose VITD on BMD in ADT-treated PCa patients compared to RDA of VITD	-
Patient Demographics	59 PCa patients (85% white; mean age = 67.6)	-
Intervention	600 IU/daily + 50,000 IU/weekly	600 IU/daily + placebo weekly
Compliance (25-OH VITD Change)	+32.0 ng/ml	+4.3 ng/ml
Safety (Grade I Hypercalcemia)	n = 1	n = 0
Total Hip BMD% Change	-1.5% (p = 0.02)	-4.1%
Femoral Neck BMD% Change	-1.7% (p = 0.06)	-4.3%
Trochanter BMD% Change	-1.0% (p = 0.10)	-2.8%
Lumbar Spine BMD% Change	-0.8% (p = 0.75)	-0.6%
Study Conclusions	Significantly greater reductions in hip BMD loss; higher doses may be necessary	A definitive phase III RCT is needed to confirm findings

CHAPTER V

DISCUSSION

The collective findings from the nine studies provide a nuanced perspective on the relationship between blood serum vitamin D levels and various aspects of prostate cancer in different contexts. Given the initial aims of the study the potential benefits of vitamin D supplementation, particularly in conjunction with exercise, showcased improvements in musculoskeletal health and vitamin D status. One of the aims was to assess the correlation between vitamin D status and osteomalacia. Research showed that high levels of vitamin D were associated with higher BMD which correlates to better muscular skeletal health for patients receiving ADT. The careful evaluation and the safety profile of vitamin D supplementation for prostate cancer patients, considering any adverse effects, potential treatment interactions, or contraindications as a result there were few incidences of drop out during treatment. And given the range of dose duration and amount the safety of the studies and vitamin D supplementation was safe. We aimed to assess the association between vitamin D supplementation and the effect on morbidity and quality of life, and overall vitamin D supplementation shows no direct benefit to treatment. However, indirect benefits for muscular skeletal health are noted and could count towards adding to patient's quality of life.

Additionally, investigations into high-dose vitamin D3 interventions and correlative analyses with other dietary components shed light on the intricate interplay between vitamin D, genetics, and biomarkers associated with prostate cancer progression. However, it is important to

acknowledge several limitations. Variability in study outcomes, sample sizes, and intervention durations makes it challenging to draw universal conclusions. The heterogeneity in patient populations, stages of prostate cancer, and treatment modalities further complicates the synthesis of evidence. Additionally, the limited follow-up periods in certain studies may not capture long-term effects accurately. Furthermore, the absence of standardized outcome measures across studies and the potential for publication bias may introduce uncertainties into the overall interpretation. While these studies contribute valuable insights, caution is warranted in generalizing the findings, emphasizing the need for more extensive, well-controlled research to establish robust associations and causal relation.

The integration of findings across these studies underscores the potential of vitamin D supplementation and exercise regimens in modulating not just musculoskeletal health but possibly influencing the progression and management of prostate cancer. The observed benefits, such as improvements in muscle strength, bone mineral density, and possibly a favorable modulation of prostate cancer biomarkers, hint at an underlying biological synergy that warrants further exploration. Specifically, the role of vitamin D in cellular differentiation, apoptosis, and the modulation of the immune response presents a compelling case for its potential utility as part of a comprehensive treatment plan for prostate cancer patients.

The variability in outcomes and responses noted across the studies also points to the critical role of genetic, environmental, and lifestyle factors in determining the efficacy of vitamin D supplementation and exercise interventions. This variability not only challenges the generalizability of the findings but also highlights the necessity for personalized medicine approaches in the management of prostate cancer. The concept of precision nutrition, which tailor’s dietary and supplement interventions to individual genetic profiles and disease states,

could be particularly relevant in optimizing the therapeutic potential of vitamin D and exercise regimens.

Moreover, the interaction between vitamin D levels and other dietary components, such as omega-3 fatty acids, as suggested by some studies, introduces an additional layer of complexity. These interactions may influence inflammation, oxidative stress, and hormonal pathways that are pivotal in prostate cancer progression. Understanding these interactions could open new avenues for dietary strategies that synergistically support cancer treatment and prevention.

CHAPTER VI

CONCLUSION

Comprehensive analysis of nine studies investigating the correlation between blood serum vitamin D levels and prostate cancer yields multifaceted insights. The combined evidence suggests that exercise, supplement adherence, and high-dose vitamin D interventions may positively influence musculoskeletal health and vitamin D status in prostate cancer patients. However, the nuanced nature of these findings underscores the importance of tailoring interventions based on individual patient characteristics and cancer stages. The implications for practice involve considering the integration of exercise and vitamin D supplementation as potential adjunctive strategies for managing prostate cancer, particularly in preserving musculoskeletal health. From a policy perspective, these results highlight the need for personalized approaches in cancer care, acknowledging the diverse effects of vitamin D interventions across patient subgroups. Future research should aim for standardized methodologies, longer follow-up periods, and larger sample sizes to establish clearer causal relationships and inform evidence-based guidelines for clinical practice. Additionally, exploring the interaction between vitamin D and other dietary components may provide a more holistic understanding of the factors influencing prostate cancer outcomes. Ultimately, these findings emphasize the complexity of the relationship between vitamin D and prostate cancer, prompting a call for continued research to refine therapeutic strategies and contribute to more targeted and effective interventions in the clinical setting.

The synthesis of evidence from the reviewed studies illuminates the intricate relationship between vitamin D supplementation, exercise, and their potential impacts on prostate cancer management. While promising, the findings necessitate cautious interpretation due to the heterogeneity of study designs, populations, and outcome measures. The insights gained underscore the importance of a holistic approach to cancer care that encompasses not only conventional treatments but also lifestyle and dietary modifications.

Future research should prioritize longitudinal studies with larger, diverse cohorts to validate the observed effects and uncover the mechanisms underlying the potential benefits of vitamin D and exercise in prostate cancer patients. This research should also strive to identify biomarkers that can predict response to vitamin D and exercise interventions, thereby enhancing the personalization of treatment strategies.

The research suggests that a comprehensive approach to the treatment of prostate cancer should involve a team of professionals from different fields, who can provide patients with nutritional advice and physical activity recommendations. Healthcare providers should have access to the necessary information and tools to assist patients in making lifestyle changes that can facilitate their treatment and improve their overall health.

As more evidence is gathered, it becomes increasingly important for policy makers and clinical guidelines to incorporate a nuanced understanding of how vitamin D can affect the outcomes of prostate cancer. This shift in both practice and policy has the potential to enhance the quality of life and clinical outcomes for prostate cancer patients, marking a significant advancement in the journey towards more personalized and effective cancer care.

REFERENCES

Alaraj, M., Alenazi, F. S., Hassan, D., & Hossain, A. (2022). Vitamin D as a drug: New therapeutic approaches. *Pharmacia*, *69*(3), 765–770. https://doi.org/10.3897/pharmacia.69.e85057

Al-Hussaini, M. H., Johnson, C. S., Muindi, J., Chadha, M. K., Silliman, C., Tian, L., Tan, W., Nesline, M., Sandecki, A., Kuettel, M. R., Mohler, J., Guru, K., & Trump, D. L. (2011). Serum 25(OH) vitamin D3 response to vitamin D3 supplementation in men with prostate cancer: Results of a randomized phase II trial. *Journal of Clinical Oncology*, *29*(15_suppl), e13060–e13060. https://doi.org/10.1200/jco.2011.29.15_suppl.e13060

Ban, J., Fock, V., Aryee, D. N. T., & Kovar, H. (2021). Mechanisms, Diagnosis and Treatment of Bone Metastases. *Cells*, *10*(11), 2944. https://doi.org/10.3390/cells10112944

Bikle, D. D. (2014). Vitamin D Metabolism, Mechanism of Action, and Clinical Applications. *Chemistry & Biology*, *21*(3), 319–329. https://doi.org/10.1016/j.chembiol.2013.12.016

Bilezikian, J. P., Formenti, A. M., Adler, R. A., Binkley, N., Bouillon, R., Lazaretti-Castro, M., Marcocci, C., Napoli, N., Rizzoli, R., & Giustina, A. (2021). Vitamin D: Dosing, levels, form, and route of administration: Does one approach fit all? *Reviews in Endocrine & Metabolic Disorders*, *22*(4), 1201–1218. https://doi.org/10.1007/s11154-021-09693-7

Calcium, I. of M. (US) C. to R. D. R. I. for V. D. and, Ross, A. C., Taylor, C. L., Yaktine, A. L., & Valle, H. B. D. (2011). Overview of Vitamin D. In *Dietary Reference Intakes for Calcium and Vitamin D*. National Academies Press (US). https://www.ncbi.nlm.nih.gov/books/NBK56061/

Carlberg, C., & Muñoz, A. (2022). An update on vitamin D signaling and cancer. *Seminars in Cancer Biology*, *79*, 217–230. https://doi.org/10.1016/j.semcancer.2020.05.018

Charoenngam, N., Shirvani, A., & Holick, M. F. (2019). Vitamin D for skeletal and non-skeletal health: What we should know. *Journal of Clinical Orthopaedics and Trauma*, *10*(6), 1082–1093. https://doi.org/10.1016/j.jcot.2019.07.004

Chi, J.-T., Lin, P.-H., Tolstikov, V., Howard, L., Chen, E. Y., Bussberg, V., Greenwood, B., Narain, N. R., Kiebish, M. A., & Freedland, S. J. (2022). *Serum metabolomic analysis of men on a low-carbohydrate diet for biochemically recurrent prostate cancer reveal the potential role of ketogenesis to slow tumor growth: A secondary analysis of the CAPS2 diet trial* [Preprint]. Cancer Biology. https://doi.org/10.1101/2021.12.29.474437

Christine M. Barnett & Tomasz M. Beer. (2011). *Vitamin D and Prostate Cancer*. 221–249. https://doi.org/10.1007/978-1-4419-7188-3_10

Cooper, R., Dasgupta, S., Li, W., Attwood, K., Kauffman, E., Kuettel, M., Johnson, C., Trump, D., & Mohler, J. (2021). PD17-04 RANDOMIZED PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY OF VITAMIN D3 REPLACEMENT IN MEN ON ACTIVE SURVEILLANCE FOR PROSTATE CANCER. *Journal of Urology*, *206*(Supplement 3). https://doi.org/10.1097/JU.0000000000001999.04

Darves-Bornoz, A., Park, J., & Katz, A. (2014). Prostate Cancer Epidemiology. In A. K. Tewari, P. Whelan, & J. D. Graham (Eds.), *Prostate Cancer* (1st ed., pp. 1–15). Wiley. https://doi.org/10.1002/9781118347379.ch1

David Feldman, R J Skowronski, & Donna M. Peehl. (1995). Vitamin D and prostate cancer. *Advances in Experimental Medicine and Biology*, *375*, 53–63. https://doi.org/10.1007/978-1-4899-0949-7_5

Deeb, K. K., Trump, D. L., & Johnson, C. S. (2007a). Vitamin D signalling pathways in cancer: Potential for anticancer therapeutics. *Nature Reviews Cancer*, *7*(9), 684–700. https://doi.org/10.1038/nrc2196

Deeb, K. K., Trump, D. L., & Johnson, C. S. (2007b). Vitamin D signalling pathways in cancer: Potential for anticancer therapeutics. *Nature Reviews Cancer*, *7*(9), 684–700. https://doi.org/10.1038/nrc2196

DiMeglio, L. A., & Imel, E. A. (2019). Chapter 13—Calcium and Phosphate: Hormonal Regulation and Metabolism. In D. B. Burr & M. R. Allen (Eds.), *Basic and Applied Bone Biology (Second Edition)* (pp. 257–282). Academic Press. https://doi.org/10.1016/B978-0-12-813259-3.00013-0

Duffy, M. J., Murray, A., Synnott, N. C., O'Donovan, N., & Crown, J. (2017). Vitamin D analogues: Potential use in cancer treatment. *Critical Reviews in Oncology/Hematology*, *112*, 190–197. https://doi.org/10.1016/j.critrevonc.2017.02.015

Food Sources of Vitamin D | Dietary Guidelines for Americans. (2024). https://www.dietaryguidelines.gov/resources/2020-2025-dietary-guidelines-online-materials/food-sources-select-nutrients/food-sources

G. Marusic, Dimitrije Jeremic, Sasa Vojinov, Natasa Filipovic, & Milan Popov. (2013). Vitamin D and prostate cancer. *Medicinski Pregled*, *66*, 259–262. https://doi.org/10.2298/MPNS1306259M

Giona, S. (2021). The Epidemiology of Prostate Cancer. In Urology Department, Frimley Park Hospital, Portsmouth Rd, Frimley, Camberley GU16 7UJ, UK, S. R. Bott, & K. Lim Ng (Eds.), *Prostate Cancer* (pp. 1–16). Exon Publications. https://doi.org/10.36255/exonpublications.prostatecancer.epidemiology.2021

Goode, E. A., Wang, N., & Munkley, J. (2023). Prostate cancer bone metastases biology and clinical management (Review). *Oncology Letters*, *25*(4), 163. https://doi.org/10.3892/ol.2023.13749

Gupta, D., Vashi, P. G., Trukova, K., Lis, C. G., & Lammersfeld, C. A. (2011). Prevalence of serum vitamin D deficiency and insufficiency in cancer: Review of the epidemiological literature. *Experimental and Therapeutic Medicine*, *2*(2), 181–193. https://doi.org/10.3892/etm.2011.205

Holick, M. F. (2006). Vitamin D: Its role in cancer prevention and treatment. *UV Exposure Guidance: A Balanced Approach between Health Risks and Health Benefits of UV and Vitamin D. Proceedings of an International Workshop, International Commission on Non-Ionizing Radiation Protection, Munich, Germany, 17-18 October, 2005*, *92*(1), 49–59. https://doi.org/10.1016/j.pbiomolbio.2006.02.014

Holick, M. F., Binkley, N. C., Bischoff-Ferrari, H. A., Gordon, C. M., Hanley, D. A., Heaney, R. P., Murad, M. H., & Weaver, C. M. (2011). Evaluation, Treatment, and Prevention of Vitamin D Deficiency: An Endocrine Society Clinical Practice Guideline. *The Journal of Clinical Endocrinology & Metabolism*, *96*(7), 1911–1930. https://doi.org/10.1210/jc.2011-0385

Iglesias-Gato, D., Thysell, E., Tyanova, S., Crnalic, S., Santos, A., Lima, T. S., Geiger, T., Cox, J., Widmark, A., Bergh, A., Mann, M., Flores-Morales, A., & Wikström, P. (2023). *Data from The Proteome of Prostate Cancer Bone Metastasis Reveals Heterogeneity with Prognostic Implications* [Other]. https://doi.org/10.1158/1078-0432.c.6529205.v1

Janoušek, J., Pilařová, V., Macáková, K., Nomura, A., Veiga-Matos, J., Silva, D. D. D., Remião, F., Saso, L., Malá-Ládová, K., Malý, J., Nováková, L., & Mladěnka, P. (2022). Vitamin D: Sources, physiological role, biokinetics, deficiency, therapeutic use, toxicity, and overview of analytical methods for detection of vitamin D and its metabolites. *Critical Reviews in Clinical Laboratory Sciences*, *59*(8), 517–554. https://doi.org/10.1080/10408363.2022.2070595

Jäpelt, R., & Jakobsen, J. (2013). Vitamin D in plants: A review of occurrence, analysis, and biosynthesis. *Frontiers in Plant Science*, *4*. https://www.frontiersin.org/articles/10.3389/fpls.2013.00136

Jarrard, D., Konety, B., Huang, W., Downs, T., Kolesar, J., Kim, K. M., Havighurst, T., Slaton, J., House, M. G., Parnes, H. L., & Bailey, H. H. (2016). Phase IIa, randomized placebo-controlled trial of single high dose cholecalciferol (vitamin D3) and daily Genistein (G-2535) versus double placebo in men with early stage prostate cancer undergoing prostatectomy. *American Journal of Clinical and Experimental Urology*, *4*(2), 17. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5069272/

Kahwati, L. C., Weber, R. P., Pan, H., Gourlay, M., LeBlanc, E., Coker-Schwimmer, M., & Viswanathan, M. (2018, April). *Appendix A Table 1, Serum Vitamin D Level Reference Ranges* [Text]. Agency for Healthcare Research and Quality (US). https://www.ncbi.nlm.nih.gov/books/NBK525404/table/app_1/

Kandutsch, A. A. (1962). Enzymatic reduction of the delta7 bond of 7-dehydrocholesterol. *The Journal of Biological Chemistry*, *237*, 358–362.

Khriguian, J., Tsui, J. M. G., Vaughan, R., Kucharczyk, M. J., Nabid, A., Bettahar, R., Vincent, L., Martin, A.-G., Jolicoeur, M., Yassa, M., Barkati, M., Igidbashian, L., Bahoric, B., Archambault, R., Villeneuve, H., Mohiuddin, M., & Niazi, T. (2021). The Clinical Significance of Bone Mineral Density Changes Following Long-Term Androgen Deprivation Therapy in Localized Prostate Cancer Patients. *Journal of Urology*, *205*(6), 1648–1654. https://doi.org/10.1097/JU.0000000000001646

Laird, E., Ward, M., McSorley, E., Strain, J. J., & Wallace, J. (2010). Vitamin D and Bone Health; Potential Mechanisms. *Nutrients*, *2*(7), 693–724. https://doi.org/10.3390/nu2070693

Lin, S.-C., Yu-Lee, L.-Y., & Lin, S.-H. (2018). Osteoblastic Factors in Prostate Cancer Bone Metastasis. *Current Osteoporosis Reports*, *16*(6), 642–647. https://doi.org/10.1007/s11914-018-0480-6

Marshall, D. T., Savage, S. J., Garrett-Mayer, E., Keane, T. E., Hollis, B. W., Horst, R. L., Ambrose, L. H., Kindy, M. S., & Gattoni-Celli, S. (2012). Vitamin D_3 Supplementation at 4000 International Units Per Day for One Year Results in a Decrease of Positive Cores at Repeat Biopsy in Subjects with Low-Risk Prostate Cancer under Active Surveillance. *The Journal of Clinical Endocrinology & Metabolism*, *97*(7), 2315–2324. https://doi.org/10.1210/jc.2012-1451

Matsushita, M., Fujita, K., Hatano, K., Hayashi, T., Kayama, H., Motooka, D., Hase, H., Yamamoto, A., Uemura, T., Yamamichi, G., Tomiyama, E., Koh, Y., Kato, T., Kawashima, A., Uemura, M., Nojima, S., Imamura, R., Mubeen, A., Netto, G. J., … Nonomura, N. (2022). High-fat diet promotes prostate cancer growth through histamine signaling. *International Journal of Cancer*, *151*(4), 623–636. https://doi.org/10.1002/ijc.34028

Mehra, R., Kumar-Sinha, C., Shankar, S., Lonigro, R. J., Jing, X., Philips, N. E., Siddiqui, J., Han, B., Cao, X., Smith, D. C., Shah, R. B., Chinnaiyan, A. M., & Pienta, K. J. (2023). *Data from Characterization of Bone Metastases from Rapid Autopsies of Prostate Cancer Patients* [Other]. https://doi.org/10.1158/1078-0432.c.6518820.v1

Mucci, L. A., Pernar, C. H., Peisch, S., Gerke, T., & Wilson, K. M. (2017). Prostate cancer incidence as an iceberg. *European Journal of Epidemiology*, *32*(6), 477–479. https://doi.org/10.1007/s10654-017-0265-8

Mukhtar, H. (2022). Diet Intervention: Choice for Cancer Prevention and Patients Survival. *DIET FACTOR (Journal of Nutritional & Food Sciences)*, 01–02. https://doi.org/10.54393/df.v3i02.57

Muscogiuri, G. (2020). Introduction to Vitamin D: Current evidence and future directions. *European Journal of Clinical Nutrition*, *74*(11), 1491–1492. https://doi.org/10.1038/s41430-020-00770-9

Naomi Smith & Alejandro Nolazco. (2013). *Vitamin D and Prostate Cancer*. 383–389. https://doi.org/10.1007/978-1-4471-2864-9_31

Office of Dietary Supplements—Vitamin D. (2024). https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., … Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ*, *372*, n71. https://doi.org/10.1136/bmj.n71

Passeri, G., & Giannini, S. (2023). Benefits of Vitamin D in Health and Diseases. *Nutrients*, *15*(11), Article 11. https://doi.org/10.3390/nu15112419

Peppone, L. J., Mustian, K. M., Peoples, A. R., Kerns, S. L., Reschke, J. E., Cole, C., Janelsins, M. C., Asare, M., Kamen, C. S., Culakova, E., Zhang, H., Fung, C., Lin, P.-J., & Mohile, S. G. (2017). A phase II RCT of high-dose vitamin D supplementation for androgen deprivation therapy (ADT)-induced bone loss among older prostate cancer (PCa) patients. *Journal of Clinical Oncology*, *35*(15_suppl), 10113–10113. https://doi.org/10.1200/JCO.2017.35.15_suppl.10113

Prabhu, A. V., Luu, W., Sharpe, L. J., & Brown, A. J. (2016). Cholesterol-mediated Degradation of 7-Dehydrocholesterol Reductase Switches the Balance from Cholesterol to Vitamin D Synthesis. *The Journal of Biological Chemistry*, *291*(16), 8363–8373. https://doi.org/10.1074/jbc.M115.699546

Rising Prostate Cancer Incidence Rates: What Can We Do About It? (2023). *Clinical Journal of Oncology Nursing*. https://doi.org/10.1188/23.CJON.109-110

Seraphin, G., Rieger, S., Hewison, M., Capobianco, E., & Lisse, T. S. (2023). The impact of vitamin D on cancer: A mini review. *The Journal of Steroid Biochemistry and Molecular Biology*, *231*, 106308. https://doi.org/10.1016/j.jsbmb.2023.106308

Shahvazi, S., Soltani, S., Ahmadi, S., De Souza, R., & Salehi-Abargouei, A. (2019). The Effect of Vitamin D Supplementation on Prostate Cancer: A Systematic Review and Meta-Analysis of Clinical Trials. *Hormone and Metabolic Research*, *51*(01), 11–21. https://doi.org/10.1055/a-0774-8809

Siddiqui, J. A., & Partridge, N. C. (2016). Physiological Bone Remodeling: Systemic Regulation and Growth Factor Involvement. *Physiology*, *31*(3), 233–245. https://doi.org/10.1152/physiol.00061.2014

Tian, X. Q., & Holick, M. F. (1995). Catalyzed thermal isomerization between previtamin D3 and vitamin D3 via beta-cyclodextrin complexation. *The Journal of Biological Chemistry*, *270*(15), 8706–8711. https://doi.org/10.1074/jbc.270.15.8706

Vitamin D Metabolism—An overview | ScienceDirect Topics. (2023, August 4). https://www.sciencedirect.com/topics/medicine-and-dentistry/vitamin-d-metabolism

Wang, L., Wu, L., Qian, C., Ju, Y., Liu, T., Chen, Y., & Wang, X. (2022). The Beneficial Effect of a Healthy Dietary Pattern on Androgen Deprivation Therapy-Related Metabolic Abnormalities in Patients with Prostate Cancer: A Meta-Analysis Based on Randomized Controlled Trials and Systematic Review. *Metabolites*, *12*(10), 969. https://doi.org/10.3390/metabo12100969

APPENDIX A

PRISMA 2020 CHECKLIST

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	
	23b	Discuss any limitations of the evidence included in the review.	
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

List of Acronyms

ADT: Androgen Deprivation Therapy

AE: Adverse Event

ANCOVA: Analysis of Covariance

BMD: Bone Mineral Density

CI: Confidence Interval

CRP: C-Reactive Protein

D2: Vitamin D2 (ergocalciferol)

D3: Vitamin D3 (cholecalciferol)

DXA: Dual-Energy X-Ray Absorptiometry

FMD: Fasting Mimicking Diet

GG: Gleason Grade

IOM: Institute of Medicine

IU: International Units

MeSH: Medical Subject Headings

OR: Odds Ratio

PSA: Prostate-Specific Antigen

PTH: Parathyroid Hormone

RCT: Randomized Controlled Trial

SE: Standard Error

VDR: Vitamin D Receptor

25(OH)D: 25-Hydroxyvitamin D

1,25(OH)2D3: 1,25-Dihydroxyvitamin D3