



زانكۆی سه‌لاحه‌دین - هه‌ولێر
Salahaddin University-Erbil

Prostate cancer and Pre diagnostic levels of serum vitamin D metabolites

Research Project
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Prepared By:
Himdad Shabaz

Supervised By:
Mr. Peshtivan Abdullah Yusif

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Dedication

This research is dedicated to

- Our/supervisor Mr. Pshtiwan Abdullah
- Chemistry department
- All men especially older and laboratory that helped us

AKNOLDGMENT

First of all, thanks for Allah to giving us the ability to do this research, a special thanking to my dear parents to supporting me always.

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We would like to express a special thanks to all members who helped us to finish this research.

Abstract

Prostate cancer is a common type of cancer in males, but it is highly treatable in the early stages. It begins in the prostate gland, which sits between the penis and the bladder. Obesity and lifestyle and dietary is associated with an increased risk of prostate cancer, Early detection of prostate cancer by PSA screening, and DRE or Biopsy or active surveillance to the patients, The association of lower 1,25-D with prostate cancer was found in men above the median age of 57 years at serum storage but not younger men and was similar in black and white men and association of elevated calcium level with patient who have prostate cancer. Primarily, surgery, radiation therapy, and proton beam therapy are the current treatment options of prostate cancer. However, chemotherapy, hormonal therapy, cryosurgery belonging to the treatment strategies.

Keywords: - prostate cancer, vitamin D or Calcium, Diagnosis, lifestyle treatment.

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List of Abbreviations

PC	Prostate cancer
BPH	Benign prostate cancer
EDCs	Endocrine disrupting chemicals
ER	Estrogen receptor
IGF-1	Insulin-like growth factor 1
PSA	Prostatic-specific antigen
DRE	Digital rectal examination
TPP-biopsy	Transperineal prostate biopsy
TRUs-biopsy	Transrectal ultrasound guided biopsy
AS	Active surveillance
LUTS	Lower urinary tract symptoms
ADT	Androgen deprivations therapy
DHT	Dihydrotestosterone
PBT	Proton beam Therapy
EBRT	External-beam radiotherapy
PLDN	Radical prostatectomy and pelvic lymphadenectomy

Introduction

(Chapter one)

1.Introduction

1.1. Cancer

Cancer is the second leading cause of mortality worldwide. Overall, the prevalence of cancer has actually increased; just in the United States alone, approximately 1,665,540 people suffered from cancer, and 585,720 of them died due to this disease by 2014 .Therefore, cancer is a serious problem affecting the health of all human societies. Unfortunately, it is a variety disease at the tissue level and this variety is a major challenge for its specific diagnosis, followed by efficacy of treatment (Hassanpour and Dehghani ,2017). In men, the highest percentages of cancer types occur in the prostate, lung and bronchus, colon and rectum, and urinary bladder, respectively. In women, cancer prevalence is highest in the breast, lung and bronchus, colon and rectum, uterine corpus and thyroid, respectively. This data indicates that prostate and breast cancer constitute a major portion of cancer in men and women, respectively (Hassanpour and Dehghani,2017). For



Figure 1: cancer cell

children, the highest percentage types of cancer disease are blood cancer, and cancers related to the brain and lymph nodes, respectively (Hassanpour and Dehghani ,2017). Cancer occurs by a series of successive mutations in genes so that these mutations change cell functions. Chemical compounds have an obvious role of forming gene mutations and cancer cells. In addition, smoking involves several carcinogenic chemicals compounds that lead to Lung cancer. Interestingly, environmental chemical substances with carcinogenic properties influence directly or indirectly the cytoplasm and nucleus of cells, and lead to genetic disorders and gene mutations, Viruses, bacteria, and radiation rays are other carcinogenesis factors, comprising about 7% of all cancers. In general, cancer disrupts cellular relations and results in the dysfunction of vital genes. This disturbance is

affective in the cell cycle, and leads to abnormal proliferation (Hassan pour and Dehghani ,2017). Protooncogenes are responsible for cell division and growth under normal condition, but become oncogenes during genetic mutation, which are most dangerous for cell existence. In addition, the lack of tumor sup- pressor genes triggers uncontrolled cells division. Normally, repair genes translate to protein and enzymes that have repairing properties and more than 30 types of detected repair proteins, Removing uracil from DNA bypasses the DNA damage and removes the main DNA lesions induced by ultraviolet light, which are essentially the functions of repair genes to successfully repair DNA(Hassanpour and Dehghani ,2017). the most common diagnosed cancers and leading causes of cancer death, for incidence in men (8 different cancer types) and for mortality in both men (8 types) and women (7 types). In men, prostate cancer is the most frequently diagnosed cancer in 112 countries, followed by lung cancer in 36 countries, and colorectal cancer and liver cancer each in 11 countries, With regard to mortality ,lung cancer is the leading cause of cancer death in men in 93 countries, in part because of its high fatality rate, followed by prostate cancer (48 countries) and liver cancer (23 countries). In contrast to men, the most commonly diagnosed cancer in women is dominated by 2 cancer sites: breast cancer (159 countries) and cervical cancer (23 of 26 remaining countries). The mortality profile in women is more heterogeneous), with breast and cervical cancer the leading causes of cancer death in 110 and 36 countries, respectively, followed by lung cancer in 25 countries(sung et all.,2021).

1.2. Prostate Gland

The prostate is a small gland in the pelvis, located underneath the bladder, surrounding the urethra and in front of the rectum and is part of the male reproductive system(Aron et all.,2016),

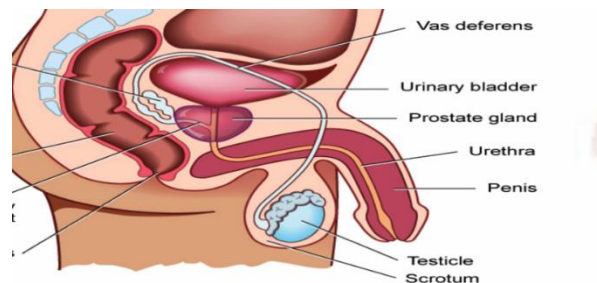


Figure2: prostate gland

It is the seat of three major causes of morbidity; benign prostatic hyperplasia (BPH), prostate cancer and prostatitis(Aron et al.,2016), It is a musculoglandular, exocrine gland that secretes alkaline fluid which constitutes about 20–30 % volume of the seminal fluid. Changes in the prostatic fluid composition and/or secretion affect sperm functions and may lead to male infertility. The gland is often associated with disorders of elderly,Besides hormones, normal prostate development and homeostasis between epithelial and stromal cells are also regulated by various growth factors. A complex interaction exists between the growth factors themselves, and, in turn, they also are regulated either by androgen or by other factors. Hence, prostate is very sensitive to any alteration, either up or down regulation, in the expression of growth factors and/or their receptors(Sharma et al.,2017).

1.3 Prostate Cancer

Prostate cancer is the second most common cause of cancer deaths in men in most developed countries, and the incidence has increased significantly over recent years. In the United States the lifetime probability of developing prostate cancer is one in six. In 1997 more than 209 900 American men were diagnosed with prostate cancer and more than 41 800 died from the disease. In England and Wales death rates have trebled over the last 30 years, one in 13 men is affected, and 20 000 cases are diagnosed each year(Mazhar and Waxman,2002)

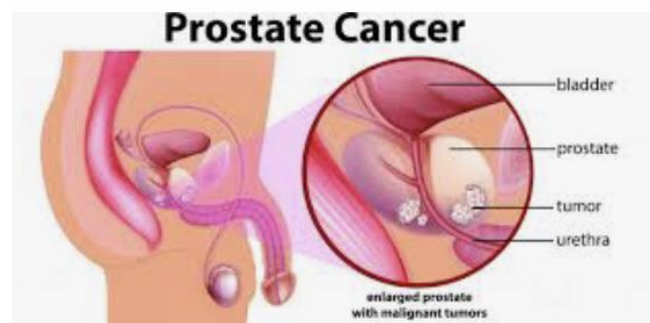


Figure 3:prostate cancer

Age is the most important risk factor. Prostate cancer is rare under the age of 40, It is estimated that less than 5% of all prostate cancer is hereditary. The risk of prostate cancer is increased by a factor of 1.3 if there is an affected father in the family, and by a factor of 2.5 if there is a brother who has prostate cancer. Approximately 95% of all prostate cancers are adenocarcinomas. Roughly 4% of all prostate malignancies arise from the transitional epithelium of the urethra or ducts as transitional cell carcinoma. Primary carcinoid tumors of the prostate, sarcomas, and

primary small cell carcinomas of the prostate are rare. Tumors of other organs may spread into the prostate(Tong et all.,2002).

1.4 Sign and Symptoms

- prostate hypertrophy.
- Erectile dysfunction (Hyun,2012)
- Hematuria(Barrass and Thursiraja,2006).
- Back, hip or pelvic pain.
- Weight loss (Wilson et all.,2011).



Figure 4: symptoms

1.5 Risk Factors :-

1.5.1 Age:

Age and household history are key danger elements for prostate cancer, and black men have a higher threat of prostate most cancers incidence and dying in contrast to guys from white or Asian backgrounds (Gan,2002).Prostate cancer incidence strongly increases with age(Gan,2002).

Older men in the United States are more likely to be diagnosed with high-risk prostate cancer and to have lower overall and cancer-specific survival. However, the evolution and progression of cancer of a given grade and stage should be expected to occur independent of chronologic age. Therefore, variation in lead-time at diagnosis and in management may explain, at least in part, observed differences in cancer specific survival. Indeed, patient age is known to strongly influence treatment decision making, with older men less likely to receive potentially curative therapy. However, the independent impact of age on prostate cancer specific survival has not been well established(Bechis et all.,2011).

1.5.2 Family History

Increased occurrence of PC has been observed in families suggesting hereditary tendency. It has been reported that 10-15% of patients with PC have at least one family member who is also affected. First degree relatives of patients have a two to three-fold increased relative risk for developing PC. The clustering of PC in families can be due to shared gene pool, exposure to common environmental factors and/or diet or perhaps due to chance alone considering the high prevalence of PC(Shad,2011).

1.5.3 Environmental Agents

One class of environmental agents that has received a lot of attention is the endocrine disrupting chemicals (EDCs). An EDC can be defined as an environmental agent that positively or negatively alters hormone activity (these are “endocrine-active”) EDCs) and ultimately leads to effects on reproduction, development, and/or carcinogenesis, particularly of reproductive organs. EDCs have been identified that elicit effects on estrogen, androgen, and/or thyroid activities. Although it has been shown that the majority of the well studied EDCs are estrogen agonists, which bind the to estrogen receptor (ER), thereby increasing estrogen activity, it has been shown that a number of EDCs affect other hormone activities. For example, it has been shown that the active metabolite of the pesticide vinclozolin is an androgen antagonist, binding to the AR and decreasing the expression of androgen-regulated genes, and an androgen agonist was identified in water downstream of pulp mills. Studies have shown that certain pesticide residues on foods, chemicals used in plastics production, and phytoestrogens in dietary plant products (e.g., soy) behave as EDCs. Exposure to EDCs can occur through ingestion of food or water or through inhalation. High level exposure to estrogen agonists is unusual, but men may have chronic exposure to low doses of a mixture of EDCs. Individuals or groups with relatively high endogenous estrogen or androgen concentrations (serum or prostate tissue levels) may have a greater susceptibility to EDC exposure, because exposure to an EDC could add effectively to the endogenous activity (Bostwick et all.,2004).

1.5.4 Physical Activity

Physical exercise may directly and circuitously limit threat of cancer, such as breast, colon, endometrium, and lung. Over the previous decade, records have emerged demonstrating the association between bodily endeavor and prostate cancer risk(Wekesa et all.,2015).

1.5.5 Diabetes

Epidemiologic evidence suggests that diabetic men have a slightly lower risk of prostate cancer than non-diabetic men, Diabetic men typically have lower levels of testosterone and insulin-like growth factor-1 (IGF-1) than non-diabetic men, and both these hormones stimulate prostate cell growth. Alterations in other growth factors, including leptin, insulin, transforming growth factor beta, vascular endothelial growth factor and tumor necrosis factor-alpha, may also help explain this association (Velicer,2007).

1.6 Diagnosis

1.6.1 DRE

While rectal examination is carried out in a systematic way to evaluate voiding dysfunction in male, its performance for preliminary detection of most cancers is limited: Most sufferers detected with PCa for the duration of screening PSA program have normal DRE. However, palpation of irregularity or nodule throughout DRE still remains an indication for prostate biopsy regardless of the stage of PSA(Descotes,2019).

1.6.2 PSA

Prostate-specific antigen (PSA), it was approved for most cancer detection. PSA checking out revolutionized our capability to diagnose, treat, and follow- up patients. In the final decades, PSA screening has led to a good sized amplify in the incidence of PC. This expanded detection has caused the incidence of advanced-stage sickness to reduce at a dramatic rate, and most lately recognized PC these days are localized tumors with a high likelihood of therapy (Nogueira ,2009).

1.6.3 Biopsy

Tissue biopsy can be obtained using either transrectal ultrasound guided biopsy (TRUS-biopsy) or transperineal prostate biopsy (TPP-biopsy). TRUS-biopsy is the most commonly offered worldwide as it can be performed in a clinic setting with local anaesthesia. TPP-biopsy is typically a day procedure often requiring general anaesthesia (Thomson et all.,2019). TPP biopsy was first described in the 1970s but has recently become more widely adopted as it has shown to be superior in sensitivity especially in detecting anterior cancers, as well as having a lower rate of sepsis compared to TRUS-biopsies (Thomson et all.,2019).

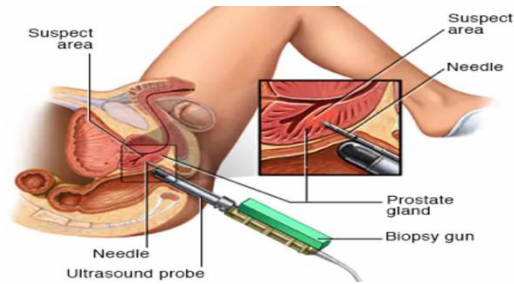


figure 5: biopsy

1.6.4 Active Surveillance

Treatment options for patients with low-grade PCa include radical prostatectomy, radiotherapy, or active surveillance. There is no significant difference in prostate cancer-specific mortality among those treatments (Hagman et al., 2019). Active surveillance (AS) for localized, low risk prostate cancer aims to reduce over-treatment and minimize the negative side effects of active treatment, such as incontinence, erectile dysfunction, strictures, and other lower urinary tract symptoms (LUTS), while retaining the option for curative treatment at the first sign of disease progression (Hagman et al., 2019). As such, patients follow up on a routine schedule with regular measurements of prostate specific antigen (PSA), digital rectal examinations (DRE), and prostate biopsies. Over the last decade, AS has joined the urologist's armamentarium as a standard treatment option. However, few studies have reported outcomes beyond ten years of follow up (Hagman et al., 2019).

1.6.4.1 Considerations for Active Surveillance as a Management Choice for Prostate Cancer

- After about 5 years, half of men undergoing active surveillance ultimately have curative treatment for their prostate cancer.
- There is a low risk for the cancer to metastasize (spread outside the prostate) or become fatal during active surveillance. The risk of metastases during active surveillance is about 4% at 10 years and the risk of death due to prostate cancer is less than 0.5%.
- Repeated prostate biopsies using ultrasound are currently the main active surveillance. Prostate biopsy can result in some discomfort. Bleeding after the

biopsy in the urine, stool, or semen, though often mild, is also common. There is also a small risk (<1%) of serious infection after each prostate biopsy (Matulewicz et al.,2017).

1-7 Treatment

1.7.1 Surgery

prostate cancer; as a substitute it is a part of the multimodality approaches. Surgery is broadly speaking advised for high risk domestically superior prostate carcinoma, Radical prostatectomy, and pelvic lymphadenectomy (PLDN) are typically applicable surgical procedure types in prostate cancer. Traditionally, RP for high-risk prostate most cancers has been discouraged because of concerns concerning the facet results such as excessive rates of superb surgical margins, threat of lymph node metastasis, and excessive fees of PSA recurrence. However, surgical procedure has been shown to be extra advisable than watchful ready for mortality, chance of nearby progression, and danger of metastasis (Chen and Zhao ,2013).

1.7.2 Radiation Therapy

After RP, radiotherapies are viewed as the second main therapeutic modalities for localized high-risk prostate cancers. External-beam radiotherapy (EBRT), this means a decrease incidence of bowel, urinary and sexual facet effects (Gay and Michalski ,2018).

1.7.3 Proton Beam Therapy

Proton beam therapy (PBT) is one the kinds of EBRT which use ionizing radiation. The primary gain of proton beam therapy is its ability to localize the radiation dosage greater precisely when compared to different sorts of radiation therapy. A particle accelerator is used to target the tumor with a beam of protons throughout the treating process. PBT approves an amazing dose distribution, with the extra gain of no exit dose. These traits make PBT as an extremely good desire for the therapy of prostate cancer (Wisnbaugh et all.,2014).

1.7.4 Cryosurgery

Cryosurgery is a cure strategy where extreme cold is applied to break unusual or diseased tissue, which include prostate tumors. In this strategy, the supercooled liquid is sprayed on the diseased tissue with the aid of the usage of liquid nitrogen as the cooling solution. For the treatment of localized low-risk prostate cancer (Wisnibaugh et al.,2014).

1.7.5 Hormonal Therapy

Androgens are regarded as the fuel for hungry prostate tumor (Brawer ,2006),Testosterone accounts for more than 90% of the systemic androgen function, and dihydrotestosterone (DHT) is its important variant (cytosolic) (Brawer ,2006).The androgen receptor (AR) is a ligand dependent transcription factor which acts in the nucleus of cells .The AR binds to testosterone and DHT with similar affinity, although DHT is a more potent androgen for structural and biochemical reasons .At normal concentrations, adrenal androgens have little effect on the prostate. Although activation of the AR by androgens is the most direct means of promoting prostatic growth, there are several surrogate pathways in prostate cancer. These pathways permit the AR to be activated, amplified, enhanced, or bypassed without androgen stimulation, thus leading to the development of prostate cancer. Androgen deprivation therapy (ADT) with either medical or surgical approach is regarded as the initial treatment for metastatic prostate cancer. The beneficial clinical effects of ADT in men with symptomatic metastatic prostate cancer are rapid and dramatic (Brawer ,2006).

1.7.6 Dietary Strategies

Like many different disorders, the interactions between man or woman genetic susceptibility, and the existence style background, such as the diet, are accountable for cancer causation. Dietary change is an important way to stop cancer, due to the fact some dietary factors may make a contribution to a limit in chance while others should motive an increase. Avoiding high fats and ldl cholesterol may assist to control or prevent prostate cancer, due to the fact dietary fat and ldl cholesterol play an essential position in the development of prostate most cancers (Matsushita ,2020).

1.8 Prostate Cancer and Pre diagnostic Levels of Serum Vitamin D Metabolites

vitamin D metabolites and their analogues influence the growth of many forms of cancer. Higher serum levels of 25-D3 and 1,25-D might be expected to reduce the risk of prostate cancer for several reasons;(a) prostate cancer

death rates are lower in regions that receive more UV needed for synthesis of previtamin D in the skin; (b) functional vitamin D receptors are present in normal prostate cells and in established prostate cancer cell lines (c);1,25-D inhibits the proliferation of cells in established prostate cancer cell lines and cultures of human prostatic epithelial cells established from normal, hyper-plastic, and malignant tissues prostate cancer (Corner et al,1993).

1,25 D has consistently been shown to inhibit prostate cancer growth and to induce cellular differentiation in laboratory experiments. 1,25 D receptors are expressed in normal and malignant prostate epithelial cells and have been shown to suppress proliferation of normal as well as LNCaP and PC-3 prostate cancer cell lines when activated. 1,25 D also stimulates production of prostate-specific antigen by LNCaP cells, which may indicate 1,25 D increases cellular differentiation (Chan and Giovannucci ,2001).

1.9 Association Between Prostate Cancer and Calcium Intake

Dairy product consumption has consistently been found to increase risk of prostate cancer in prospective epidemiologic studies. Dairy products are the major food source of calcium in Western populations, where nearly all of the previous studies were conducted. While the underlying mechanism is unknown, there are several nutrients that may contribute to the observed association between dairy products and prostate cancer, such as calcium, saturated fatty acids, protein, and phosphorus. The focus of this paper is on the role of calcium on prostate cancer risk.

There is biologic plausibility for a role for calcium in prostate carcinogenesis. Intracellular calcium pools have been shown to control prostate cancer cell growth and susceptibility to apoptosis .Although tightly maintained, small alterations in calcium homeostasis can result in increased proliferation, differentiation and apoptosis in prostate cancer cells .Calcium homeostasis is maintained in part by the calcium-sensing receptor .a G protein-coupled cell-surface glycoprotein that is expressed in PC-3 cells and may play a role in malignant progression of prostate tumors (Lesley and Alvin,2010).

In addition to the experimental evidence, prospective epidemiologic studies of calcium and prostate cancer also support a positive association ,particularly for high levels of intake (>2000

mg/day) .High levels of calcium intake are typical in Western populations, where dairy product intake is high ($\approx 14\%$ consume ≥ 3 servings/day) and calcium supplementation is common ($\approx 48\%$).The strong correlation between dairy and calcium intake in previously studied populations made it difficult to evaluate the effects of calcium, independent of residual confounding from dairy intake or supplement use, or sociodemographic factors related to dairy intake and/or supplement use (Lasley and Alvin,2010).

Chapter two

(Material and method)

2.1 Materials

Twenty samples were used male gender, the age were between 45-77 years. 10 people who had prostate cancer and 10 people were normal as control, blood was taken. serum was made to do calcium and vitamin D.

2.2 Methods

Calcium test (normal range is 8.5-10.2 mg/dL) was measured by Fuji film

Vitamin D blood test measures the level of 25(OH)in your blood (normal range is between 20and 40ng/ml) was measured by Maglumi-800

2.3 Data Analysis

Data were analyzed by bar chat A bar chart uses bars to show comparisons between categories of data. These bars can be displayed horizontally or vertically. A bar graph will always have two axes. One axis will generally have numerical values, and the other will describe the types of categories being compared.

The comparison you want to make will help determine whether to display the bars vertical or horizontal. You would need to decide whether the data you are trying to represent has an intuitive direction or not.

And we used vertical bar chart in our research to compare between to values, in every Vitamin D and calcium test for prostate Cancer that can show decrease or increase during this cancer and obviously showed in result.

2.4 Data Collection:

We collected samples from people who had prostate cancer or we collected report in laboratory specific those people who had prostate cancer for two tests (calcium and vitamin-D) level ,at first to take blood from veins carefully without any failure due to not hemolysis later after centrifuge because we need serum, and we handled our samples in refrigerator until we can use it and work with it for our research, in university laboratory we just had titration for those two tests not good equipment so also we prefer taking reports about prostate cancer patients in labs who are believable and have high quality works ,so we can depend on them for our tests

Chapter three

Result and discussion

3- Result and Discussion

The main purpose of this study to investigate whether Serum Vitamin D and calcium are decreased compared to normal people.

3.1 Effect of Vitamin D on the Prostate Cancer

The body breaks vitamin D down into the compound calcitriol. calcitriol may slow the growth of cancers, including prostate cancer. However, many of these studies examine cancer cells in a laboratory or in animals rather than the human body. Vitamin D also plays an important role in immune function, Vitamin D deficiency may increase inflammation. which is a risk factor for many diseases, including cancer. Research on the specific benefits of vitamin D for treating or preventing prostate cancer has produced mixed results. People who had prostate cancer have lower decreased Vitamin D level compared to normal people

Table1: patients with vitamin D test

Patient number	Vitamin D
Patient 1	15ng/ml

Patient 2	13ng/ml
Patient 3	10ng/ml
Patient 4	14ng/ml
Patient 5	8ng/ml
Patient 6	12ng/ml
Patient 7	8ng/ml
Patient 8	13ng/ml
Patient 9	9ng/ml
Patient 10	6ng/ml

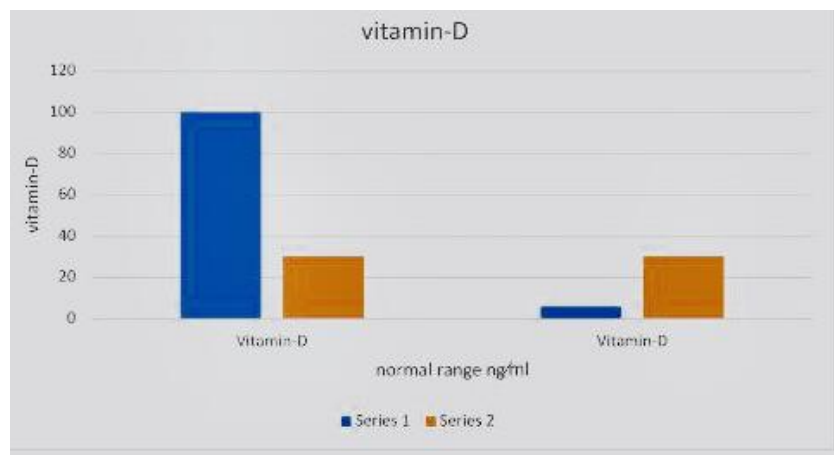


Table 2: PSA before pretreatment

Patient number (nanakali hospital)	PSA (pretreatment)
Patient 1	145
Patient 2	62
Patient 3	770
Patient 4	320
Patient 5	23
Patient 6	79
Patient 7	106

Table3: PSA after treatment

Patient number	PSA treatment
Patient 1	14
Patient 2	20

Patient 3	11
Patient 4	18
Patient 5	16
Patient 6	22
Patient 7	16

3.2 Effect of Calcium on the Prostate Cancer

Men with elevated serum calcium levels might have an increased risk of fatal prostate cancer, according to a new American study. Previous research has shown that both calcium and parathyroid hormone, which controls serum calcium levels, can promote growth and metastasis of prostate cancer cells.

Too much calcium in your blood can weaken your bones, create kidney stones, and interfere with how your heart and brain work

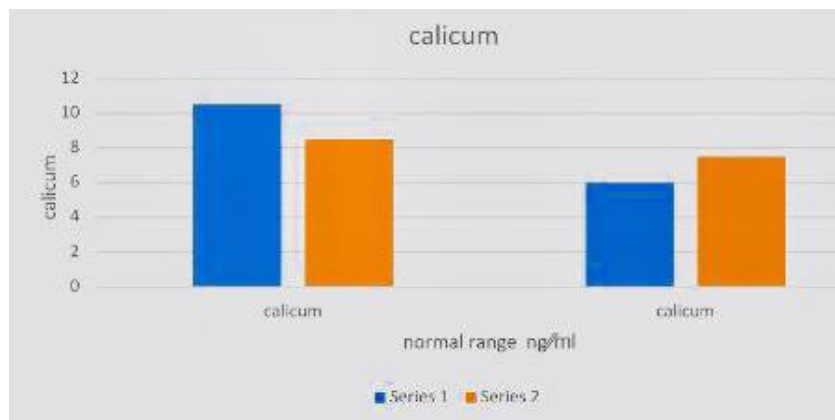


Figure 1.6.3: Effect of calcium on the prostate cancer

People who had prostate cancer have higher or elevated calcium level compared to normal people.

Table3: patient with elevated calcium level

Patient number	Elevated Calcium results
Patient 1	10.3mg/dl
Patient 2	10.5mg/dl
Patient 3	10.4mg/dl

Patient 4	10.6mg/dl
Patient 5	10.8mg/dl
Patient 6	10.7mg/dl
Patient 7	10.9mg/dl
Patient 8	11.3mg/dl
Patient 9	11.1mg/dl
Patient 10	11.4mg/dl

But in some situations, calcium level will decrease with patient who has prostate cancer and this cancer affected bone so due to this level of calcium in such person's will decrease

Table4: patient with decreased calcium level

Patient number	Decreased calcium results
Patient 1	7mg/dl
Patient 2	5.8mg/dl
Patient 3	6.3mg/dl
Patient 4	4.7mg/dl
Patient 5	8.2/mg/dl
Patient 6	5.3mg/dl
Patient 7	6.1 mg/dl
Patient 8	7.5mg/dl

Patient 9	5.9mg/dl
Patient 10	4.9mg/dl

Chapter four

Conclusion and recommendation

4.1 Conclusion

It was concluded that there is a potential for using Serum vitamin D, and Calcium for prostate cancer, the decrease of vitamin D and calcium in serum detection are marker for having prostate cancer, and other factors like lifestyle and physical activity and genetic.

4.2 Recommendation

1-it's very crucial to check out your health yearly.

2-it's important to test Vitamin D and calcium.

3.be careful of signs and symptoms before it gets more dangerous

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