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Association of Vitamin D_3 with some Biochemical Parameters in Benign Prostatic Hyperplasia Patients

A Thesis

Submitted to Council of the College of Science, University of Anbar in partial fulfillment of the requirements for the M.Sc. Degree in Chemistry

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بسم ميحرلا نمحرلا هللا

﴿ ولَقَدۡ ءَاتَيۡنا داوُد و سلَيۡمَٰنَ عِلۡ وقَاَ ٱلۡحَ لِلَّهِ ٱلَّذِي فَضَّلَنَا علَىٰ كَثِيرٖ مِّنۡ عِبادِهِ ٱلۡمُؤۡمِنِينَ ﴾

صدق هللا العظيم

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Supervisors Certification

We certify that this thesis entitled)**Association of vitamin D3 with Some biochemical parameters in Benign prostatic hyperplasia patients** (was prepared by **Mohammad Zaki Taha** under our supervision in the department of Chemistry , College of Science at the university of Anbar as a partial requirement for the degree of master in Chemistry .

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Dedication

To the teacher of humanity, my role model and my beloved messenger, Muhammad, may God bless him and grant him peace.

To the one who taught me patience and diligence and spent her life for my comfort and success ... my beloved mother.

To my father, my support and arms in this life.

To my dear sister and my dear brothers...

To all my family and friends ...

I present to you my humble work study...

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Summary

Benign prostatic hyperplasia is a common disease in nearly half of men between the ages of 51 and 60year, and this percentage increases to 90% of men over the age of 80 year. The study included (87 samples) divided into two groups of 25 healthy and 62 Benign prostatic hyperplasia patients. The study was conducted at Yarmouk Teaching Hospital (Baghdad) and the study period was from December 2019 to March 2020.

By diagnosing vitamin D3, a similar deficiency in vitamin D3 was observed for the same target age group during the study and by observing healthy people of the same age group who had normal levels of vitamin D3 and found that 76% of them did not suffer from Benign prostatic hyperplasia problems. Through studying the variables, it was found that there is a negative relationship between the same statistical significance between vitamin D levels and prostatic specific antigen levels; and this relationship between them supports the relationship and the effect of vitamin D in reducing inflation, as prostate antigen levels rise in the case of inflation. The study of the relationships between the rest of the variables also showed a negative relationship between the level of the ratio of free prostate-free antigen to the total and the prostate-specific antigen; and this relationship is very important in differentiating between benign and malignant tumors in the prostate.

The results of the study showed significant differences between the group of patients suffering from Benign prostatic hyperplasia and the group of healthy people in each of (vitamin D_3, PSA, PTH, Serum Zinc,

Age), while there were no significant differences between the two groups in each of (BMI, Testosterone, Calcium Ion, Phosphorus Ion, Serum Iron).

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List of Abbreviation

Abbreviation	Description
AR	androgen receptor
ATP	Adenosine triphosphate
AMP	Adenosine monophosphate
BPH	Benign prostatic hyperplasia
BMI	Body mass index
BOO	bladder outlet obstruction
CaSR	calcium-sensing receptor
Ca	Calcium
CYP2R1	cytochrome P450 family 2 subfamily R member 1
CYP1A1	Cytochrome P450 Family 1 Subfamily A Member 1
CDK	Cyclin-dependent kinases
DRE	Digital Rectal Exam
DHT	Dihydrotestosterone
DNA	Deoxyribonucleic acid
DBP	vitamin D binding protein
DHEA	dehydroepiandrosterone
ECF	Extracellular fluid
ER	Estrogen receptor
FSH	Follicle-stimulating hormone
FGF23	Fibroblast growth factor 23
f PSA	Free prostatic specific antigen
FGF1	fibroblast growth factor-1
FGF2	fibroblast growth factor-2
FGF7	fibroblast growth factor-7
Fe^{+2}	Ferrous
f/t PSA	Free to total prostatic specific antigen
HMG-CoA	3-hydroxy-3-methyl-glutaryl-coenzyme A reductase
H_2O_2	Hydrogen peroxide
INSIG-1	Insulin Induced Gene 1
KLK3	Kallikrein Related Peptidase 3
LH	Luteinizing hormone
LUTS	Lower urinary tract symptoms
PIN	Prostatic intraepithelial neoplasia
PCa	Prostate cancer
POR	Cytochrome P450 reductase
PTH	Parathyroid hormone
P450	cytochrome P450

RANKL	Receptor activator of nuclear factor kappa-B ligand
SHBG	Sex Hormone Binding Globulin
SREBP	Sterol regulatory element-binding proteins
SCAP	Security Content Automation Protocol
S1P	Sphingosine-1-phosphate
TGF-b	Transforming growth factor beta
t PSA	Total prostatic specific antigen
UVB ray	ultraviolet B rays
VDR	Vitamin D Receptor
ZIP 1	Zinc transporter
Zn	Zinc
25[OH]	25-hydroxyvitamin D3

Chapter One

Introduction and Literature review

Introduction

Benign prostatic hyperplasia)BPH) is one of the most common health problems in men older than 50 year .It reaches 50% in this age group; at the age of 80 year, 90% of them will have an enlarged prostate. It may cause urinary retention, with a risk of frequent infections of the urinary tract, and sometimes renal impairment BPH symptoms include[(1)]: Medications, minor surgeries, and prostate surgery. The most common solutions for men with benign prostatic hyperplasia or lower urinary tract symptoms (LUTS) that lead to bothersome problems such as frequent urination, the need for night urination, urinary tract stenosis, and incomplete bladder emptying, in emptying and intermittent urine stream[(2)].

The patient may experience many symptoms, but one of them mainly disturbs him. Urinary tract infections, prostate inflammation, prostate cancer, bladder cancer, urethral stricture and bladder stones. It can also cause LUTS. Malignant disease can be excluded by conducting a digital rectal examination (DRE), a prostate blood test, and a urine test. If these tests are normal, benign prostate is the most likely cause of LUTS. For men over 50 years old, a high Prostatic- specific antigen (PSA) or nodular prostate can be an indication of prostate cancer.

Microscopic hematuria with urinary symptoms can be an indication of bladder or prostate cancer [(3)]. Numerous studies have shown a relationship between deficiency of vitamin D and benign prostatic hyperplasia, including those that were done on Chinese men over 50 years of age [(4)]. Another study using Vitamin D as a treatment for an enlarged prostate was able to stop the growth of the prostate volume

within 84 days in men over the age of fifty with a prostate volume of 140 ml [5].

During this period, vitamin D deficiency is considered an epidemic. The first reason for vitamin D deficiency is that many people do not know that moderate exposure to sunlight is the main source of vitamin D for most people. Very few foods naturally contain vitamin D, and diets fortified with vitamin D are often insufficient to meet the vitamin D requirements of a kids and adults. Vitamin D deficiency leads to rickets in children, which increases and worsens osteoporosis, osteoporosis and fractures in adults [6].

Here an important point must be pointed out when studying vitamin D. Classic endocrine feedback loops ensure the regulation of blood calcium. Calcium in the extracellular fluid (ECF) binds and activates the calcium sensing receptor (CaSR) on the parathyroid cells, leading to an increase in intracellular calcium. This in turn leads to a reduced parathyroid hormone (PTH) release. Hypocalcemia leads to the opposite sequence of events, namely, lowered intracellular calcium and increased PTH production and secretion[7]. Parathyroid hormone rapidly increases renal calcium reabsorption and over hours to days, enhances osteoclastic bone assimilation and liberates both calcium and phosphate from the skeleton. PTH also increases fibroblast growth factor 23 (FGF23) release from mature osteoblasts and osteocytes. PTH stimulates the renal conversion of 25-hydroxyvitamin D (25[OH]D) to 1,25(OH)2 D , likely over several hours, which in turn will augment intestinal calcium absorption[8]. Prolonged hypocalcemia and exposure to elevated PTH may also result in 1, 25(OH) 2 D mediated calcium and

phosphorus release from bone. These effects restore the (ECF) calcium to normal and inhibit further production of PTH and 1, 25(OH) 2D. Additionally, (FGF23) can be released from bone by 1, 25(OH) 2D and can in turn reduce 1, 25(OH) 2D concentrations. (FGF23) has also been reported to decrease PTH production. When (ECF) calcium is in the hypercalcemic range, PTH secretion is reduced and renal 1, 25(OH) 2 D production is decreased. In addition, the elevated calcium per se stimulates the renal CaSR , thus inducing calciuria. Therefore, suppression of PTH release and 1, 25(OH) 2D synthesis and stimulation of the renal CaSR lead to reduced renal calcium reabsorption, decreased skeletal calcium release, and decreased intestinal calcium absorption, resulting in the normalization of the elevated (ECF) calcium [(9)].

Other studies show that patients suffer from the primary hypogonadism, testosterone replacement allows the development of normal prostate growth and BPH. It is also known that in males with prostate diseases (such as prostate cancer or BPH), emasculation treatments or androgen deprivation lead to reduced prostate bulk and improved urinary function in some patients[(10)].

Zinc is an important component of prostate health, as imbalances in the level of zinc in the body lead to various lesions such as BPH, PIN, and PCA [(11)]. Because it accumulates a large part of it in the soft tissues in the body This is unique Ownership is held in BPH, but is lost in prostatic malignancy, which is involved changes in zinc and its vectors carcinogenesis [(12)].

More than a century ago, it was reported that cholesterol crystals and other fatty acids accumulated in solid tumors [13]. Almost 78 years ago, Swyer showed an increase in cholesterol in prostate tumors compared to normal prostate tissue [14]. Among human beings and animal models that support a relationship between cholesterol in prostate tissue and secretions with benign and malignant prostate tumors [15]. Recent epidemiological evidence suggests that a modern Western diet, which contains large levels of cholesterol and other fatty substances, promotes the development of prostate cancer [16]. In line with this idea, inhibition of the prolonged cholesterol synthesis pathway by pharmacological intervention is associated with a lower risk of advanced prostate cancer [17]. Additionally, epidemiological and clinical studies have found positive correlations between hypercystic condition and for blood and symptoms of the lower urinary tract (LUTS) suggestive of benign prostatic hyperplasia (BPH) Therefore became possible physiological mechanisms underlying pathological linking cholesterol and prostate diseases currently active area of scientific research [18].

1.1 Prostate gland

The prostate is a gland in the male reproductive system. For adults, it's the size of a nut. The prostate is located in the pelvis. Inside it lies the urethra coming from the bladder, which is called the prostate urethra, and which merges with the ejaculation duct [19] (Figure1.1).

Anatomically, the prostate can be divided in two ways: by region or by lobe. It does not have a capsule. Instead of an integrated fibromuscular band surrounds it. [20]. Sheathed in the pelvic floor muscles, which contract during ejaculation. The prostate also contains

some smooth muscles that also help flush out semen during ejaculation.The average normal prostate weight in adult males is about (11 grams), usually between (7 and 16 grams). The size of the prostate can be estimated by the formula (0.52 x length x width x height). A volume of more than 30 cm^3 is considered an enlarged prostate (prostatomegaly). A study stated that the size of the prostate among patients with a negative biopsy was significantly related to weight and height (body mass index), so it is necessary to control weight [21].

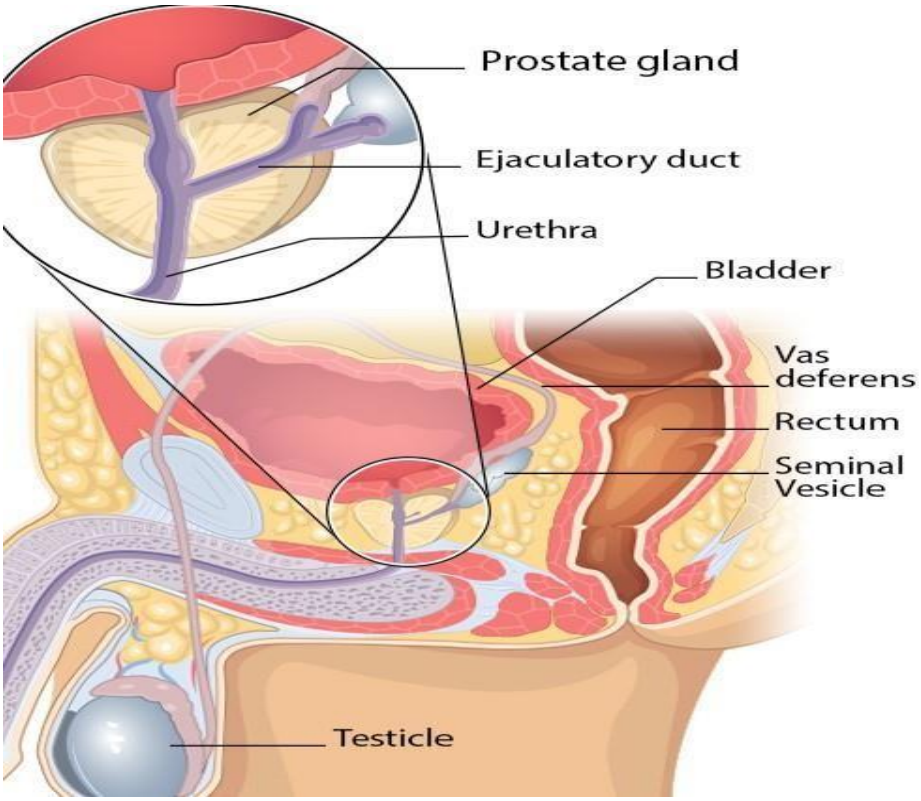

Figure1.1: This graph shows the location of the prostate, just in front of the rectum and just below the bladder [20].

1.2 Benign Prostatic Hyperplasia (BPH)

Benign Prostatic Hyperplasia(BPH) is an age-related and piecemeal neoplastic condition of the prostate gland. The (BPH) is a histologic diagnosis that back to the spreading of smooth muscle and epithelial cells meanwhile the prostatic transition zone (Figure1.2) [(22)]. The exact etiology is unknown; nevertheless the similarity between BPH and the embryonic morphogenesis of the prostate has led to the supposition that BPH may result from a ―reawakening‖ in adulthood of embryonic induction operations.

An enlarged gland has been suggested to contribute to the total lower urinary system symptom (LUTS) symptom in at least two ways: First, the direct bladder outlet (BOO) obstruction from the enlarged tissue (fixed component) and the second from increased smooth muscle strength and resistance within the enlarged gland (dynamic component) [(23)]. BPH may only be known histologically. Benign prostatic hyperplasia within the clinical setting can be characterized by symptoms of the urinary tract (LUTS). There is no causal correlation between benign and malignant prostatic hypertrophy [(24)].

Clinically evident BPH represents a large health problem for older men, because of its negative effects on the nature of life. Benign prostatic hyperplasia occurs by 50% in men between the ages of 50 – 60 year and this percentage increases with age. The spread rate of BPH is 10.3%, with a general incidence rate (of 15 per 1000 man-years), increasing with age (3 per 1000 at age 46-50 years, to 38 per 1000 at 76-80 year). For a symptom-free man at the age of 46 year, Clinical BPH risk for the next 30 year [(25)], Treatment for the BPH incurs a substantial economic load,

with estimated annual costs of up to US$4 billion in the United States in 2006, and Average annual treatment costs of (€858 per patient) in Europe in 2003 [26] . Owing to the demographic transformation towards an elderly population, costs emerging from lower urinary tract symptoms secondary to benign prostatic hyperplasia are likely to increase entirely. Surgical treatment is recommended if reservation treatment failure or for patients with complexity related to benign prostatic hyperplasia, and is performed in more than (100 000 men) annually in the USA [27]. Transurethral amputation of the prostate (TURP) is still the optimal surgical solution in most patients [28].

There have been many of studies show the fact that clinical BPH is a gradual disease. The Olmsted county study showed that with every year there were deteriorations in symptom scores, Urine flow, and increases in prostate volumes depending on the transrectal ultrasound scanning (TRUS). The risk of acute urinary retention increased with flow average below 12 ml/sec and with glands greater than 30ml. Studies have also show that those with larger prostates (40 ml) and with serum PSA larger than (1.4 ng/ml) were more possible to develop acute urinary retention [29]

Although LUTS secondary to (LUTS/BPH) is not frequently a life-threatening stipulation, the impact of LUTS/BPH on quality of life They can be large and should not be underestimated. When the effect of BPH-linked LUTS on quality of life (QoL) was studied in a number of societal societies, for many, the most important drivers for seeking treatment were the severity and degree of discomfort associated with the symptoms. These were also important considerations when assessing BPH and determining when to refer to treatment [30]. Traditionally, the

main goal of treatment has been to relieve the annoying LUTS caused by an enlarged prostate. Lately, treatment has additionally focused on changing disease progression and preventing complications that can be associated with BPH [31].A wide variety of drug classes are used including alpha-adrenergic remedies, anticholinergics and plants. Choosing the right medical treatment for BPH is really complex and always changing. In troublesome LUTS management, it is important for healthcare providers to familiarize themselves with the complex dynamics of the bladder, bladder neck, prostate and urethra [32].

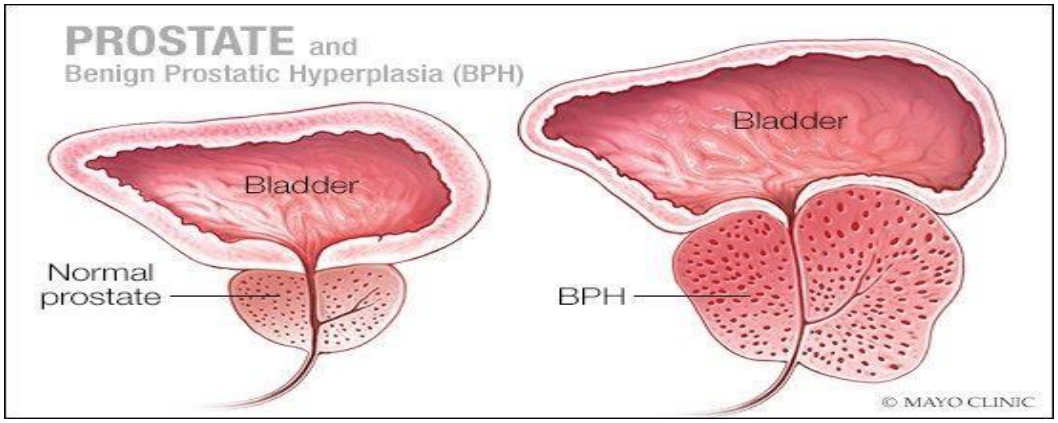

Figure1.2: The difference between a normal prostate and an enlarged prostate and its effect on the urethra [22].

1.2.1 Pathophysiology

Despite its high prevalence and social and economic impact, the pathophysiology of BPH is not fully understood. For example, it is still largely unknown why some men have a prostate 40 grams while others have a prostate 200 grams. Here, we review several pathophysiology (focusing on the androgen pathway) and the most important clinical

aspects of BPH. Pathological mechanisms leading to LUTS are more complex only than BPH and include many urodynamic patterns (for example, hyperactivity), changes within the infrastructure of urinary and bladder surgery, anticholinergic receptor status, pelvic ischemia and many others [(33)].

The prostate, like other sexual dependency tissues, is stimulated in its (growth, maintenance, and secretory function) by the presence of certain hormones and growth factors. Above all these are testosterone. The blood testosterone is under the control of the pituitary gland (LH / FSH) testis (testosterone) axis of the hormone. Testosterone comes from the testicle (95%) And the adrenal gland (5%) It is a large androgen that stimulates prostate growth. The average plasma testosterone concentration is about 600 ng / ml. Serum testosterone levels remain somewhat steady between 25 and 60 years old, however they decrease gradually after that. Although testosterone is the primary plasma androgen, it also works as a hormone in that the most active androgen type in the prostate is dihydrotestosterone (DHT) [(34)].

The hormonal regulation of BPH depends on the presence of the (androgen and estrogen receptors). In addition, the activity of the enzyme 5α-reductase plays an important role in causing benign prostatic hyperplasia. Androgen receptors (AR) are widely expressed in benign epithelium and adjacent stroma. AR action in prostate tissue is enhanced by stimulants that may interact with N-terminal domains, DNA binding and / or ligand for the receptor. . In order to understand the working principle of therapeutic intervention in a benign prostate, it is important to emphasize that 5α-reductase is responsible for androgen synthesis

more effective, DHT. Therefore inhibitory approaches in BPH primarily target (5α- reductase).The BPH tissue includes (oestrogen receptor α) in the stroma and (oestrogen receptor β) in the epithelium[35].

1.3 Vitamin D

Vitamin D is a fat-soluble steroid hormone accountable for increasing intestinal absorption of magnesium, calcium, and phosphate, and many other biological effects [36]. It is derived either by photosynthesis, where 7-dehydrocholesterol is converted into vitamin D by ultraviolet sunlight or of nutritional origin. Vitamin D3 nutritional (from most natural sources) or D2 (most of which are of pharmaceutical origin) actually originates from photosynthesis in living organisms. The vitamin D content of most food products is somewhat low, except for some fats. Moreover, its stated content has not always been verified by accurate and updated measurements [37]

1.3.1 Sources of vitamin D

The main natural source of vitamin is the synthesis of cholecalciferol in the lower layers of the cutaneous epidermis through a chemical reaction based on exposure to sunlight .especially (UVB rays) [38]. Cholecalciferol and ergocalciferol can be taken both from diet and from nutritional supplements [39]. Only a few foods, such as fatty fish meat, naturally contain large amounts of vitamin D [40]. In the United States and other countries, cow's milk and plant-derived milk substitutes are fortified with vitamin D, as well as many breakfast cereals. Mushrooms exposed to ultraviolet light contribute to beneficial amounts of vitamin D [41]. Vitamin D from the diet, or from skin synthesis, is biologically inactive. The protein enzyme hydroxyl must convert it to the active form.

This is done in the liver and kidneys. Since vitamin D can be manufactured in sufficient quantities by most mammals exposed to sufficient sunlight, it is not a major nutritional factor, although technically it is not a vitamin. Alternatively, it can be considered a hormone, with the activation of the vitamin D hormone leading to the active form, calcitriol, which results in effects by a nuclear receptor at multiple sites [42].

1.3.2 Vitamin D metabolism

In the blood circulation, vitamin D is transported mainly by the vitamin D binding protein (DBP), a serum glycoprotein secreted by the liver [43]. Vitamin D itself is biologically inert and hydroxy bound with 25 hydroxy vitamin D (25 (OH) D_3) in the liver. Serum 25 (OH) D_3 is measured to assess the state of vitamin D, because this isoform is the major metabolite of vitamin D that better reflects the amount of vitamin D from all sources. Additionally, 1-hydroxylation of 25 (OH) D occurs mainly in the kidneys and leads to the formation of an active hormone of vitamin D 1, 25 $(OH)_2 D_3$ [44].

Endocrine production of 1, 25 $(OH)_2 D_3$ is tightly regulated by bone and mineral metabolism. For example, the production of 1, 25 $(OH)_2 D_2$ is stimulated by the parathyroid hormone (PTH) and stabilized by fibrous cell growth factor 23 (FGF-23) with the primary goal of maintaining adequate serum calcium levels through the effects of 1, 25 $(OH)_2 D_3$ on the kidneys, intestines and bones. Therefore, serum concentrations 1, 25 $(OH)_2 D_3$ are not a good measure for the supply or placement of vitamin D. Effects of 1, 25 $(OH)_2 D_3$ can be substituted and parasrin because the expression 25-hydroxy vitamin D-1α-hydroxylase (1α-hydroxylase). It

has been reported in many extracellular cells, including cells of the cardiovascular system [45]. Local tissue production of 1,25 $(OH)_2$ D appears to mainly depend on the availability of the circular circuit 25 (OH) D_3, but production of 1, 25 $(OH)_2 D_3$ is also regulated by other factors such as cytokines [46]. Finally, 1, 25 $(OH)_2 D_3$ exerts its biological effects by binding to VDR3, which is expressed almost everywhere. However, tissue distribution and the specific type of VDR have not been completely resolved throughout the body, and not all studies have detected VDR expression in tissues such as the skeleton, heart, or smooth muscle. After cellular VDR is activated by ligand binding and transition to the nucleus, VDR interacts with activator.

The elements of the vitamin D response in the promoter region of the target genes, and therefore, regulate about 3% of the genome. The degradation of 1, 25 $(OH)_2 D_3$ and other vitamin D products begins with hydroxyl 24 (Figure 1.3), an enzymatic process that is stimulated, for example, by activating the VDR itself, thus preventing vitamin D poisoning as part of the self-loop regulation[47].

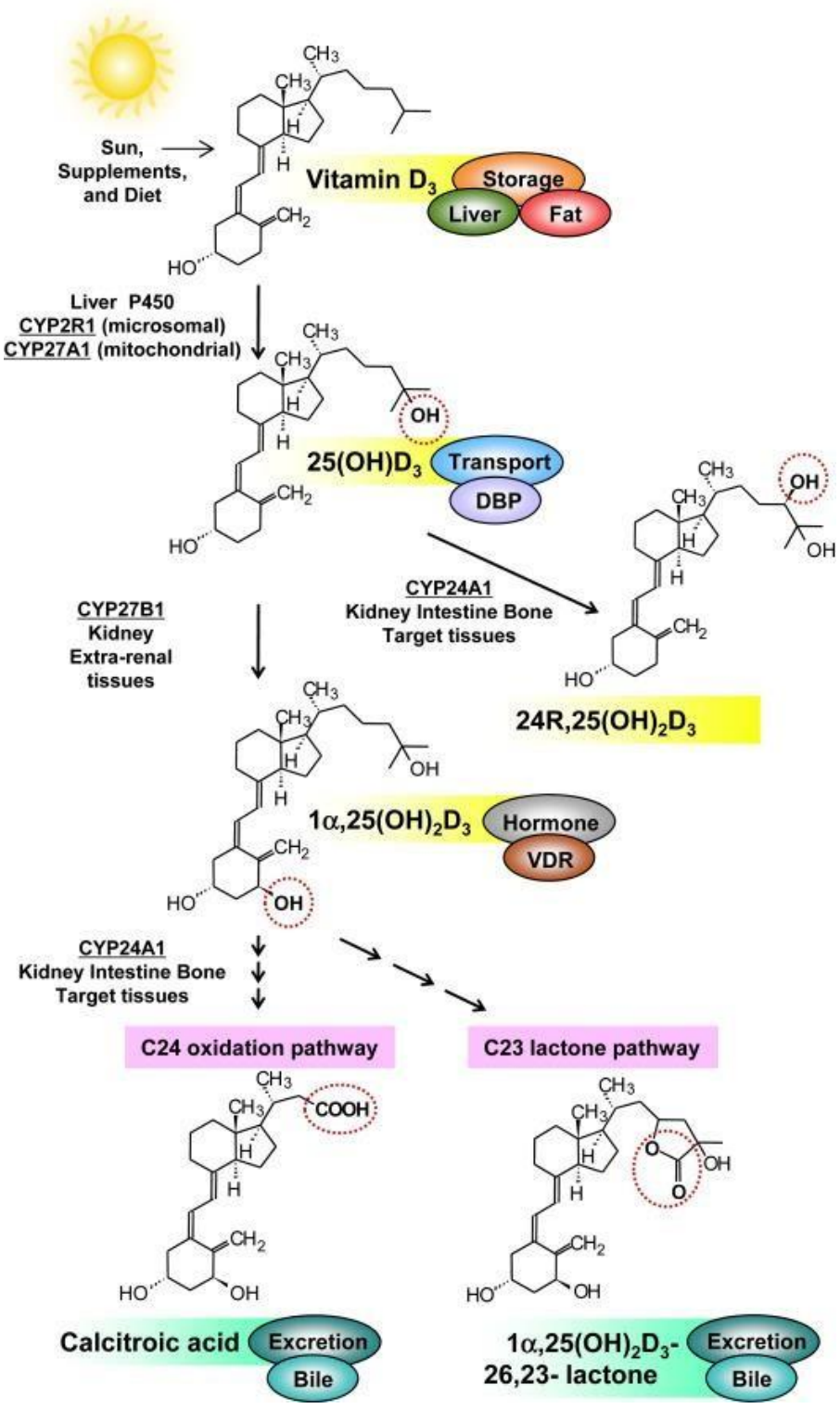

Figure 1.3. Pathways of vitamin D activation and inactivation. Vitamin D3 absorbed from the diet or synthesized in the skin on exposure to UVB is stored in the liver and fat [43]

1.3.3 Role of vitamin D in human metabolic processes

Vitamin D3 is first metabolized in the liver to 25-hydroxy-vitamin D (25-OH-D or calcidiol) and then in the kidneys to produce 1, 25 $(OH)_2 D_3$ (or calcitriol), a biologically active hormone. There are 1, 25 $(OH)_2 D_3$, like all vitamin D metabolites, in the blood of a vitamin D binding protein, which is a specific α globulin. 1, 25 $(OH)_2 D_3$ is thought to act on target cells similar to the way the steroid hormone works. The free hormone crosses the plasma membrane and interacts with a specific nuclear receptor known as the vitamin D receptor, which is a protein bound by DNA and zinc finger protein with a molecular weight of 55,000 Dalton [48].

The ligand receptor complex binds to a specific component that responds to vitamin D, and to its associated transcription factors (for example, the retinoid X receptor), promotes transcription of mRNAs that denote calcium transport proteins, bone matrix proteins, or cell cycle proteins [49]. As a result of these processes, 1, 25 $(OH)_2 D_3$ stimulates intestinal absorption of calcium and phosphate and mobilizes calcium and phosphate by stimulating bone resorption [50].

The common purpose is to restore blood calcium and phosphate levels back to normal when ion concentrations are low. Recently, attention has focused on other cellular actions of 1, 25 $(OH)_2 D_3$. With the discovery of 1, 25 $(OH)_2 D_3$ receptors in many non-target classical tissues such as the brain, various cells derived from bone marrow, skin, and thymus gland, etc. (7). The view has been expressed that 1, 25 $(OH)_2 D_3$ stimulates the fusion and differentiation of macrophages [51]. This effect has been widely interpreted to mean that the normal role of 1, 25

(OH) $_2$ D_3 is to stimulate the formation of bone cells from colonized granulocyte-forming units in the bone marrow. The 1, 25 (OH) $_2$ D_3 also inhibits the production of interleukin-2 in activated T-lymphocytes [(52)], an effect that indicates that the hormone may play a role in modifying immunity in vivo. Other tissues (such as the skin) are directly affected by the external administration of vitamin D, although the physiological significance of these effects is not well understood. The pharmacological effects of 1, 25 (OH) $_2$ D_3 are profound and have led to the development of vitamin D analogues, which have been approved for use in cases of excessive reproduction such as psoriasis [(53)].

In the treatment of benign prostatic hyperplasia where the active hormonal form of vitamin D, 1α, 25-dihydroxy vitamin D3 (calcitriol) plays a crucial role in cellular proliferation and differentiation of normal and malignant cells. The VDRs are expressed not only in the normal state but also in prostate cancerous and precancerous conditions [(54)], and therefore calcitriol has the potential for therapeutic treatment for benign prostate cancer and prostate cancer.

However, the therapeutic application of calcitriol is insufficient due to the additional effects of hypercalcemia and hyperphosphatemia. Therefore, calcitriol analogues have been developed that maintain anti-reproductive properties but do not cause side effects of hypercalcemia *in vivo* [(55)]. Chronic inflammation is now specific to benign prostatic hyperplasia together, with group hormonal conditions, prostatic hyperplasia and lower urinary tract symptoms (LUTS). Calcitriol can also boost innate immunity and regulate adaptive immune responses, as they can be helpful in treating inflammatory diseases such as BPH [(56)].

In general, VDR triggers can modify the LUTS dynamic component and perform anti-inflammatory activities. Thus, this class of factors can symbolize an interesting therapeutic alternative to drug therapy for BPH. Vitamin D has amazing potential as a curing agent in the treatment of benign prostatic hyperplasia. However, there have not yet been extensive clinical trials using vitamin D or its analogues to treat benign prostatic hyperplasia.

At present, many isotopes of vitamin D are screened, but none have been found to be effective without causing side effects. Since vitamin D works primarily via VDR, the multiple forms of the VDR gene may affect the function of Vitamin D and individual genetic characteristics must be considered when using Vitamin D to treat BPH. This may increase the effectiveness of vitamin D analogues and reduce side effects[57]. In calcium homeostasis 1, 25 $(OH)_2 D_3$ works in conjunction with parathyroid hormone (PTH) to produce its benefits. Effects on plasma levels of ionized calcium and phosphate [58].

The physiological ring begins with calcium sensing by the calcium receptor in the parathyroid gland [59]. When the level of calcium ionized in the plasma decreases, the PTH is secreted by the parathyroid gland and the highly-regulated renal enzyme 25-OH-D1-α-hydroxylase is stimulated to obtain more 1, 25 $(OH)_2 D_3$ of the large circular pool 25-OH -D. The resulting increase in 1, 25 $(OH)_2 D_3$ (with higher PTH) leads to an increase in the transport of calcium within the intestine, bones, and kidneys. All of these events raise the levels of calcium in the plasma to normal, which in turn are felt by the calcium receptors in the parathyroid gland. The additional secretion of PTH is discontinued not only by the

action of the calcium feedback, but also by a short feedback loop involving 1, 25 (OH) $_2$ D_3 that directly suppresses PTH synthesis in the parathyroid gland. Although this model overstates the simplification of events involved in calcium homeostasis, it is easy to see that there must be sufficient 25-OH-D_3 to provide a suitable two-dimensional synthesis of 1,25 (OH) and then an appropriate level of calcium In the plasma. And that a lack of vitamin D will lead to insufficient synthesis of 25-OH-D and 1, 25 (OH) $_2$ D_3, insufficient calcium balance and a high level of PTH (called: secondary hyperthyroidism)[60]. From showing the role of vitamin D, it is clear that a dietitian can focus on plasma levels 25) OH(D_3 and PTH to gain insight into the state of vitamin D. Not clarified but also important is the last point of the physiology of the action of vitamin D, i.e. calcium and calcium phosphate. It is suitable in plasma, which provides the raw materials for bone mineralization [61]

1.4 Prostatic- specific antigen

Prostatic- specific antigen (PSA), a glycoprotein enzyme encoded in humans by the Kallikrein Related Peptidase 3)KLK3(gene. The PSA is a member of the peptidase-linked peptidase family and is secreted by the epithelial cells of the prostate gland. The PSA is produced for ejaculation, it liquefies semen and allows sperm to swim freely [62]. It is also believed to be beneficial in dissolving cervical mucus, allowing sperm to enter the uterus [63]. The PSA is present in small amounts in the serum of men with a healthy prostate, but it often rises in the presence of prostate cancer or other prostate disorders. PSA is not a unique indicator of prostate cancer, but it may also detect prostatitis or benign prostatic hyperplasia [64]. The PSA is a widely used tumor marker. Although

normal prostate cells can express PSA, Prostate cancer)PC) tissues release about 10 times the serum PSA from normal or benign prostatic tissue [65]. The PSA release is believed to be associated with disruption of the normal prostatic membranes occurring in the computer. There is a biological difference to PSA in the general population and no PSA value excludes the possibility of the computer being detected when a biopsy is taken. Serum total PSA level of 4.0 ng / ml is often considered the upper limit for normal and is frequently used as a referral threshold for further examination and biopsy.

An estimate of PCP prevalence was established in men with PSA values below 4.0 ng / mL in a previous study in the prevention of prostate cancer [66]. Men who were in the control group - had never had a PSA of 4.0 ng / ml or greater, or had an abnormal digital rectal examination (DRE), or had a prostate biopsy or prostatectomy during referral - even - a biopsy was taken in end of follow-up for 7 years. Fifteen percent of men (449/2950), all of them with a total serum PSA less than 4.0 ng / ml, were found to have a computer in biopsy. In this group, the risk of PC was also found to increase as the PSA level increased, from 6.6% for PSA values of 0.5 ng / ml or less to 26.9% for PSA levels between 3.1 and 4.0 ng / ml [67].

Having accurate prostate volume (PV) measures is often important in clinical and epidemiological studies of benign prostatic hyperplasia and lower urinary tract symptoms as PV is associated with an increased risk of acute urinary retention and the need for treatment [68]. Currently available techniques to assess PV tend to be unsuitable for large studies of healthy men. While digital rectal tests (DREs) are easy to perform and

useful for PV estimation, the authors of previous studies have indicated that this method underestimates the actual PV. Estimate for transrectal ultrasound (TRUS) or imaging techniques are the gold standard for accurate PV evaluation [69] . Unfortunately, these procedures are costly, time consuming, and uncomfortable, which limits their use of large-scale epidemiological studies. A less intrusive alternative method of assessing PV may be beneficial for research studies, especially among men without major clinical symptoms in urology.

Prostate levels of the prostate-specific antigen (PSA) are currently used clinically as a tool for screening prostate tumers. Additionally, the researchers also reported that serum PSA levels show a positive relationship with PV [70], and thus provide a means for PV estimation among men without prostate cancer. Creating simple PV prediction equations based on serum PSA level and age [71].

1.5 Testosterone

1.5.1 The biosynthesis of testosterone

Testosterone is synthesized by an enzymatic sequence of steps from cholesterol [72], within 500 million Leydig cells located in the interstitial space between the testicles between the seminal tubes, which make up about 5% of the size of the mature testicle . Cholesterol is mostly formed by synthesizing de novo from acetate, although pre-cholesterol from either cholesterol ester stores or extracellular supply of low-density lipoproteins also contributes [73]. The biosynthesis of testosterone includes two multifunctional cytochrome P-450 complex that includes hydroxylones and side chain cleavages (cholesterol side chain splitting

[CYP11A1 or P450scc producing C20 and C22 hydroxylase and C20,22 lease activity]] and 17-hydroxylase / 1720 liazole or CYP17 P450c17 which works on C17 hydroxyl and then expels two carbon atoms (20 and 21) covering 21 to 19 carbon structures]) with 3 and 17b-hydroxy steroid dehydrogenase and 4,4 isomerase. The tissue selective regulation of 1720 lyase activity (active in the gonads but not active in the adrenal gland) independently of the activity of 17 hydroxylase (active in all steroidal tissues) is a major branch of steroid pathways.

Both activities are present in one multifunctional protein with the path flow direction determined by coenzyme co-factors, in particular electron supply from NADPH via P450 oxidoreductase (POR), and membrane-related flavoprotein providing various roles such as reductase, and cytochrome b5 [(74)]. Additionally, some extra-androgenic synthesis of testosterone and dihydrotestosterone has been described from circulating weak androgenic-weak adrenal DHEA within specific tissues [(75)]; however, the net contribution of adrenal androgens to circulating testosterone in men is insignificant [(76)], on Although it makes a much larger relative contribution to circulating testosterone in women [(77)]. Dynamic synthesis pathways for testosterone and action.

In men, the biosynthesis of testosterone occurs almost exclusively in mature Leydig cells by the enzymatic sequences shown. Cholesterol is predominantly produced by the de novo synthesis pathway of acetyl coA with the lutein hormone that regulates the rate-determining step, and the conversion of cholesterol to pregnenolone in the mitochondria, while the remaining enzymatic steps occur in the smooth endoplasmic reticulum. Steroidal pathways D5 and D4 on the left and right, respectively.

Testosterone and its androgenic metabolite, dihydrotestosterone, directly exert biological effects by binding to androgen receptors and indirectly through the aromatization of testosterone to estradiol, which allows working via binding to estrogen receptors (ER). Androgenic and ERs are members of the super-steroid nuclear receptor super-family with a very homogeneous structure mostly different in ligand C-terminal binding domain [78].

1.5.2 Androgen secretion

Testosterone is excreted at adult levels during three periods of male life: transiently during the first three months of intrauterine life (coinciding with male genital tract differentiation), during early neonatal life such as increased androgen hormone in the perinatal period (with still physiological importance Unspecified), and continuously after puberty to maintain urbanization. Dramatic physical changes in puberty are caused by surprising increases in testicle secretion from testosterone, with ~ 30 times higher levels prevailing in children before puberty and in women or men neutering stemming from sources outside the testicle. After middle age, there are gradual decreases in circulating testosterone plus an increase in the levels of globulin and gonadotropin [79] with the absence of these trends until late aging.

Testosterone, like other lipophilic steroids that are excreted from steroidal tissues, leaves the testicle by spreading a concentration gradient across cell membranes into the bloodstream, with fewer lymphoid and tubular fluids appearing. After male puberty, more than 95% of the circulating testosterone is derived from testicle secretion and the rest

arises from an extra-precursor transformation with negligible intrinsic masculine strength such as dehydroepiandrosterone and androstenedione. These weak androgens, which originate mostly from the adrenal cortex, form a large circulating tank of precursors for conversion to biologically active sexual stimulants in external tissues including the liver, kidneys, muscles, and adipose tissue. Unlike women where adrenal androgens are the main source of biologically active androgen precursors, internal adrenal androgens contribute slightly to irritation for men directly and the rest of androgens and tissues after medical or surgical castration have little biological effect on androgen-sensitive prostate cancer [80].

On the contrary, adrenal androgens make a relatively larger contribution to the prevalent testosterone concentrations in children and women (~ 5% of men) as testosterone in the blood is derived almost equally from direct and indirect gonadotrophs from the peripheral exchange of the adrenal androgens precursors. External dehydroepiandrosterone in physiological substitution doses of 50 mg / day orally is not able to provide adequate blood testosterone for androgen replacement in men but produces dose-dependent increases in estradiol circulation in men and hyperandrogenism in women [81].

1.5.3 The role of testosterone in benign prostatic hyperplasia

In the prostate, testosterone is converted into the most effective DHT hormone with high levels of 5-reductase, and high levels of DHT are what boost the androgen signal in the prostate. It can be allowing the prostate to function normally and undergo age-related growth, even with low levels of circulating testosterone [82]. As a result, despite the increasing prevalence of low levels of testosterone in the blood among

elderly men, benign prostatic hyperplasia is common. Moreover, the beneficial effects of dutasterideon BPH could be expected before that, even with low levels of testosterone. The absence of a consistent pattern of treatment differences between placebo and dutasteride across a set of basic testosterone levels evaluated in these analyzes supports this hypothesis. The 52 men with the lowest BST levels of less than 150 ng / dL behaved differently from the rest of the study community: they were slightly older; had a larger prostate and increased prostate volume over time with placebo; and had a higher BMI, increased The occurrence of impotence, change in libido, decreased SFI, and a greater decrease in sexual function over time with placebo [83].

These results can be a manifestation of obesity-related metabolic syndrome and merit further examination in other data sets. In conclusion, sexual function in men is partly dependent on testosterone in the blood, but many men have normal sexual function in low-circulating androgen levels. Serum testosterone test failure to predict impotence in men with benign prostatic hyperplasia. On the other hand, the androgenic stimulation of the prostate is largely independent of testosterone in the blood, at least in the range of testosterone. This explains why benign prostatic hyperplasia occurs in men who can be considered hypogonadism. By maximizing the 5-reductase activity, dutasteride is effective in treating BPH, regardless of testosterone levels in the blood [84].

1.5.4 Growth factors and their role in prostate enlargement

Growth factors are small peptide molecules that stimulate, or in some cases inhibit, the cell division and differentiation processes. Cells that

respond to the growth factors have on their surface receptors specific for that growth factor that in turn are linked to a variety of transmembrane and intracellular signaling mechanisms. Interactions between growth factors and steroid hormones may alter the balance of cell proliferation versus cell death to produce BPH (Figure 1.4) Subsequent to the first description of the basic fibroblast growth factor in BPH by Story [85]. A variety of growth factors have been characterized in normal, hyperplastic and neoplastic prostatic tissue[86]. In addition to bFGF (FGF-2), acidic FGF (FGF-1), Int-2 (FGF-3), keratinocyte growth factor (FGF-7), transforming growth factors (TGF-b) and epidermal growth factor have been implicated in prostate growth. TGF-b is a potent inhibitor of proliferation in normal epithelial cells in a variety of tissues. In models of prostatic cancer, there is evidence that malignant cells have escaped the growth inhibitory effect of TGF-b. There is mounting evidence of interdependence between growth factors, growth factor receptors and the steroid hormone milieu of the prostate. Although data on the absolute level of growth factor and growth factor receptors in hyperplastic as opposed to normal tissue are conflicting, it is likely that growth factors play some role in the pathogenesis of BPH [87].

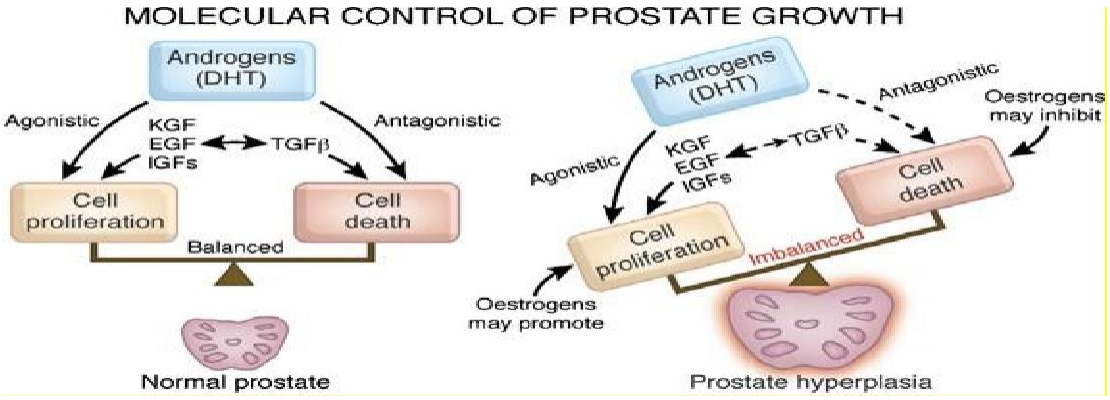

Figure 1.4: Balance between growth stimulatory and inhibitory factors involved in cellular homeostasis in the prostate gland [85].

1.6 Parathyroid hormone

Parathyroid hormone is a polypeptide that is synthesized and formed in an active form within the parathyroid gland. The primary composition formed is pre-pro-PTH, 115-peptide amino acids to form pro-PTH consisting of 90 amino acids. It is then slit again, again in the amino peripheral part to form the active parathyroid hormone made up of 84 amino acids. This is the primary hormone that is stored, secreted, and works in the body [88]. The tuning, split, and storage process is estimated to take less than an hour. Active PTH secretion can happen as quickly as a few seconds when low calcium is detected in the blood. The secretion mechanism is by expelling the cells, a process in which the hormone is released through a membrane vesicle that is transferred to the cell membrane, and the hormone is released after the vesicle fuses with the outer membrane. The serum half-life for activated PTH is a few minutes and is quickly removed from the serum by the kidneys and liver [89].

1.6.1 The regulatory role of Parathyroid hormone

Parathyroid hormone regulates calcium in the blood through its effect on the bones, kidneys and intestines in the bone, PTH promotes the release of calcium from the large reservoir in the bone. Bone reabsorption is the natural destruction of bone by osteoblasts, which are indirectly stimulated by PTH. The stimulation is indirect because the osteoblasts do not contain receptors for the hormone PTH. Instead, the PTH binds to the bone cells, which are the cells responsible for bone formation [90]. Binding stimulates osteoblasts to increase their expression of RANKL and prevent their secretion of Osteoprotegerin (OPG). The

free OPG competitively binds to RANKL as a decoy receiver, which prevents RANKL from interacting with RANK, which is a RANKL receiver. RANKL binding to RANK (facilitated by a decrease in the amount of OPG available to bind excess RANKL) stimulates these bone precursors to fuse, forming new osteoblasts, which ultimately promotes bone re-uptake. Another mechanism for regulating these pathways as PTH does is by estrogenic. Estrogen blocks the production of TNF T cells by regulating T cell differentiation and activity in the bone marrow, thymus and peripheral lymphoid organs. In the bone marrow, estrogen regulates the proliferation of hematopoietic stem cells through an IL-7 dependent mechanism [(91)].

In kidney, approximately 250 mmol of calcium ions are filtered into glomerular filtration a day. Most of this (245 mmol / d) is reabsorbed from the tubular fluid, leaving about 5 mmol / d excreted in the urine. This reabsorption occurs throughout the tubule (mostly, 60-70% of it in the nearby tubule), except for the thin part of the Henley ring. Circulating parathyroid hormone only affects the reabsorption that occurs in distal tubes and renal canals [(92)].

However, a more important effect of PTH on the kidneys is the inhibition of phosphate reabsorption (HPO_4^{-2}) from the tubular fluid, which leads to a decrease in the phosphate concentration in the plasma. Phosphate ions form water insoluble salts with calcium. Thus, a decrease in the concentration of phosphates in the blood plasma (for a total calcium concentration) increases the amount of ionized calcium [(93)]. The third important effect of PTH on the kidneys is their stimulation to convert 25-hydroxy vitamin D into 1,25-dihydroxy vitamin D (calcitriol),

which is released into the bloodstream. This last form of vitamin D is the active hormone that stimulates calcium absorption from the intestine. By the kidneys, PTH promotes the absorption of calcium in the intestine by increasing the production of vitamin D. Activated vitamin D stimulation occurs in the kidneys. PTH regulates 25-hydroxyvitamin D_3 1-alpha-hydroxylase, which is the enzyme responsible for 1-alpha hydroxylation for 25-hydroxy vitamin D, and converts vitamin D into its active form (1,25-dihydroxy vitamin D). This stimulant form of vitamin D increases intestinal absorption by calbindin (as Ca^{+2} ions).

PTH was one of the first hormones to be shown to use the G-protein system, adenylyl cyclase II. PTH reduces the reabsorption of phosphates from the proximal tubules, which means that more phosphate is excreted through the urine. However, PTH promotes phosphate absorption from the intestine and bone in the blood. In the bones, calcium is released slightly more than phosphate than broken bones. In the intestine, both calcium and phosphate are absorbed by increasing activated vitamin D. The end result of PTH release is a small decrease in the phosphate concentration in the blood [(94)].

1.7 Free prostate-specific antigen (f PSA)

Most PSA in the blood is bound to serum proteins. A small amount that is not bound to protein and is called "Free PSA". In men with prostate cancer, the free (unrestricted) PSA ratio decreases to the total PSA. The risk of developing cancer increases if the free-to-total ratio is less than 25%. The lower the percentage, the higher the risk of prostate cancer [(95)]. Measuring the free PSA-to-gross ratio seems especially

promising to eliminate unnecessary biopsies in men with PSA levels between 4 and 10 ng / ml. However, both total and free PSA increase immediately after ejaculation, and slowly return to baseline levels within 24 hours [96] Important vital signs for detecting prostate cancer, guiding decisions about prostate biopsies, and showing a way to monitor disease progression [97]. Total PSA (tPSA) includes unrestricted and restricted (or complex) PSA forms; refers to the sum of all forms of serum detectable immunoglobulin, because FCAA became known to signs in 1991[98], several studies have shown that PSA has a high sensitivity but low-specification city, which can lead to unnecessary biopsies, especially in patients with benign diseases, and carcinomas intervene when tPSA is raised moderately [99].

1.7.1 Free/Total prostatic specific antigen ratio(f/tPSA ratio)

The PSA exists in three forms. The main form of serum immune PSA is an alpha-1 associated with alpha-1 antichymotrypsin, approximately 75% of the total circulatory PSA. The PSA associated with alpha-2 macroglobulin is in less than 0.1% (not detectable by commercial test), while the free PSA (enzymatically inactive form) is 5-50% in serum [100]. The main drawback of PSA is its low specificity, especially in patients with a total PSA concentration in the "diagnostic gray area" (total PSA concentration range is 4-10 ng / ml).

In order to achieve greater privacy in identifying PSA, various indexes have been developed: Age-specific PSA, PSA density, PSA acceleration, PSA density in the transition region, free and total PSA ratio, and ratio (fPSA%). In addition to the PSA total, the most useful

diagnostic indicator for distinguishing benign prostatic hyperplasia is Free to Total PSA (PSA free / PSA total) [101]. Research on this ratio is extremely important in patients who have a negative rectal examination. Free to total PSA ratio (% fPSA) is a method that increases the sensitivity and specificity of PSA in diagnosing prostate cancer, and its easy identification allows diagnosis of disease, or malignant operations. The likelihood of detecting prostate cancer, depending on the% fPSA, increases with the patients age.

Prostate cancer is a progressive progressive disease of the prostate, which constantly increases the release of PSA and the majority of patients with reduced FPSA by less (less than 10% free PSA, and more than 90% PSA binding) with prostate cancer [102].

After the development of immunoassay, it was proved that the fPSA% was lower in men with prostate cancer. Men with continuously elevated PSA levels should assess fPSA. If the percentage is less than 8%, the risk of developing prostate cancer is approximately 80%.%FPSA in the blood was found as an effective indicator for distinguishing BPH diagnosis from prostate cancer, and was therefore used to distinguish between benign and malignant diseases of the prostate gland in order to improve the poor privacy of total PSA examination in serum alone [103].The importance of these tests shows in the free PSA sensitivity of the overall PSA ratio in diagnosing prostate cancer, to link the diagnosis to the sensitivity and specificity of% fPSA, to determine the specificity and sensitivity of% fPSA in different sectors - values in detecting prostate cancer, and emphasizing the importance of results% fPSA, without examining the prostate[104].

1.8 Zinc

Zinc is an essential mineral, including growth before and after birth. Zinc deficiency affects approximately two billion people in the developing world and is associated with many diseases. In children, lack of developmental delay, sexual maturity, susceptibility and diarrhea are caused. Enzymes containing zinc atom are dispersed in an interactive center in biochemistry, such as alcohol dehydrogenase in humans. Excess zinc consumption may lead to copper ataxia, lethargy, and deficiency[105].

Zinc is a necessary tracking component needed for normal prostate function. Irregular zinc concentration, i.e. either increased or lower can lead to different prostate lesions such as BHP, PIN, and PCA but the results of the research are conflicting. The concentration of prostate zinc is reduced in Pca but high levels of zinc in the blood are shown in BPH and PIN and decrease in Pca.

Zinc exerts its influence through various carrier proteins and the variation in carrier protein can lead to BPH or Pca. The prostate is the accumulation of zinc jacket product member contains a highest level of zinc more than others tissues [106]. ZIP1 protein is responsible for the active transport of zinc in the prostate cells. Zinc plays an important role to change cell metabolism in order to produce citrate which is an important component of semen's apoptosis. Zinc process accumulation and change in metabolism the production of citrate is an ineffective energy and prostate cells sacrifice enormously energy (ATP) to complete this task [107]. Zinc is necessary micronutrients required for more than 300 various cellular processes [108] including DNA and protein synthesis,

enzyme activity, and intracellular signals, prostate epithelium The cells have a distinctively high airway sugar degradation, low and high respiration rates citrate secretions [109]. Zinc imposes apoptosis effects suppression of the tumor Zinc ions contribute (II), It is unique to the human prostate glandular epithelial cells have a unique. The ability to accumulate high levels of zinc[110].

This is an essential feature to install activity of m-aconitase so that it can citrate accumulate prostate secretion fluids, a major function of prostate gland. These results in truncation Krebs cycle with result it has produced ATP that produces from oxidizing citrate. Also prevents the accumulation of zinc Oxidation of the mitochondrial station Breathing. Additional metabolic effects Zinc accumulation leads to anti Reproductive effects by inducing them apoptosis. Zinc accumulation prevents, too invasive / migration activities in malignant tumors Prostate cells. Anti-reproductive effects and effects on the invasion Migration occurs by activating zinc specific signal paths within cells[111]. As a result, these opposite effects are imposed Tumor procedures by zinc. Growing body empirical evidence supports those high Zinc levels are necessary for the prostate the health. Possible mechanisms include effects of zinc on inhibition final oxidation, induction apoptosis, mitochondrial apoptosis suppression of NFκB activity [112].

1.9 Iron

Iron is a transition metal d-block, and like many of these minerals, many oxidation states can be assumed. The most common types are iron (Fe^{+2}) and triple iron (Fe^{+3}). The oxidation potential of iron can be greatly modified by the nature of the bonded links. This has major implications for physiology because other oxidation states, such as ferryl (Fe^{+4}), can be transiently generated as major feedstocks during mineralized oxidative transitions. Likewise, other transitional elements such as copper and manganese are able to participate in biological redox reactions [113]. Iron can be present in multiple oxidation states, which is necessary for the transport of an electron, and for its binding to biological lignin bonds[114].

The probability of reducing iron ranges from 1000 to 50550 mV, depending on the legend environment, while the range of other transport elements is narrower [115]. By exploiting the states of oxidation, the state of the electron's rotation and the potential for oxidation, biological systems can adjust the chemical reaction of iron to suit physiological needs. An example of iron for living things is an indispensable example. A cofactor of many blood proteins and non-heme iron-containing proteins, including many enzymes.

Blood proteins are involved in many biological functions such as binding and transporting oxygen (hemoglobin), oxygen metabolism (catalase and peroxidase), cellular respiration and transfer of electrons (cytochrome). Non-heme iron-containing proteins are important for basic cellular processes such as DNA synthesis and cell proliferation Variation (Ribonucleotide reduction), gene regulation, drug metabolism, and steroid synthesis [116]. Early in evolution, before oxygen appeared as an

abundant component of the atmosphere, anaerobic cells acquired soluble iron in relative ease. Moreover, the oxidation and reduction cycle of ferric iron and iron in the presence of H_2O_2 and O_2, which are produced physiologically during air respiration and enzymatic reactions, produces hydroxyl radicals (Fenton reaction). These, in turn, attack and damage cellular molecules easily. Thus, despite its abundance, obtaining and transporting iron is a challenge for cells and organisms due to its low solubility and high toxicity. To overcome these problems, single-celled organisms such as bacteria synthesize "siderophores", which are of low molecular weight and chelating factors of iron that capture iron outside the cell and transfer it to the cell. In contrast, extracellular mammalian cells acquire carrier proteins [117].

1.10 Effects of trace elements (zinc and iron) on benign prostatic hyperplasia

Trace elements have basic physiological functions such as maintenance and regulation of cell function, regulation of genes, activation or inhibition of enzymatic reactions, and regulation of membrane function. The primary or toxic properties (mutagenic, carcinogenic) of trace elements depend on the need or tolerance of tissues, respectively [118]. Insufficient or excessive accumulation, in addition to the imbalance of trace elements, may cause disturbance of cell functions and may lead to cellular degeneration or death or, conversely, intense proliferation [119]. Consequently, the results of the increase or decrease in trace elements and disturbances in their relationships in the benign excessive tissues may highlight the role of these disorders in the etiology of benign prostatic hyperplasia.

Unfortunately, the data regarding the effects of tracker ingestion on the risk of benign prostatic hyperplasia are inconsistent and provide a very mixed picture. However, there is evidence of decreased bioavailability of minerals in the elderly [120]. Proponents of the –deficiency theory‖ believe that due to lifestyle, dietary and nutritional habits, and the physiological effects of aging, older males are usually prepared for conditions of copper, zinc, and other antioxidant deficiencies, which can increase their susceptibility to infection BPH [121], a significant positive correlation was observed between age and some contents of trace elements in the non-excessive prostate [122]. In addition to Zn androgen dependence is found for some contents of other trace elements in the prostate [123].

High zinc concentrations within the chest are likely to be one of the main factors affecting prostate cell proliferation [124]. We have recently shown a very pronounced tendency for age-related exponential increase in the Zn mass fraction as well as an increase in Zn / Fe, Zn / Rb and Zn / Sr ratios in the prostate [125].

Moreover, a significant positive correlation was observed between the Zn prostate and the contents of other trace elements. Thus, it is possible that in addition to Zn, trace elements such as Br, Fe, Rb, and Sr also play a role in the pathophysiology of the prostate. This work had three goals. The first was to assess the contents of, Fe,and Zn in serum for patients who had BPH, using 109Cd derived from radionuclide-induced radioactive energy (EDXRF). The second goal was to compare levels of trace elements in BPH glands with those in the non-disordered prostate of healthy men over 40 years old. The third objective was to

calculate and compare Zn / trace content content ratios in the normal range and BPH [126].

1.11 Cholesterol

Cholesterol is an organic molecule. It is a steroid (or modified steroid), and is a type of fat [127]. Cholesterol is bioavailable by all animal cells and is an essential structural component of animal cell membranes. Cholesterol also acts as an indicator of the biosynthesis of steroid hormones, bile acid and vitamin D. In vertebrates, hepatocytes usually produce the largest quantities. It is absent among prokaryotes (bacteria and archaea), although there are some exceptions, such as mycoplasma, that require cholesterol for growth [128] .Cholesterol is essential for all forms of animal life, as each cell is able to generate it via a complex 37 step process. This begins with the mevalonate or HMG-CoA reduction pathway, which is the goal of statin drugs, which includes the first 18 steps. This is followed by an additional 19 steps to convert the resulting lanostrol into cholesterol [129].

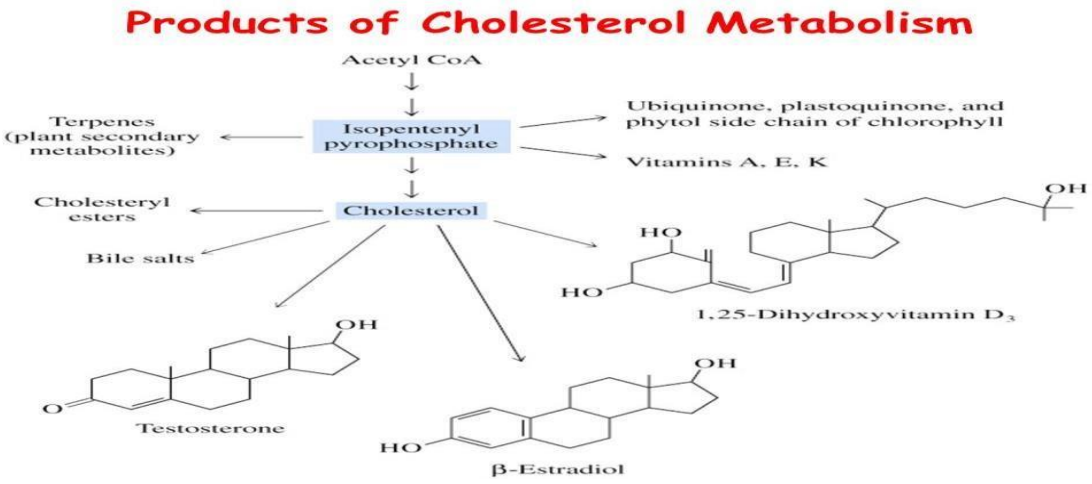

Figure1.5: Biosynthesis of steroid hormones, bile acid, and vitamin D as a metabolic cholesterol product [128].

1.111.Biosynthesis of cholesterol and its regulating process

The vital synthesis of cholesterol is directly regulated by the existing cholesterol levels, although the respective heterogeneous mechanisms are only partially understood. Eating larger amounts of food leads to a net decrease in internal production, while a decrease in food intake has the opposite effect. The main regulatory mechanism is the sensing of intracellular cholesterol in the endoplasmic reticulum by the SREBP protein (regulatory steroid binding protein 1 and 2) [(130)]. In the presence of cholesterol, SREBP is bound to two other proteins: SCAP (SREBP) and INSIG-1. When cholesterol levels drop, INSIG-1 is separated from the SREBP-SCAP compound, which allows the complex to transfer to a Golgi apparatus. Here SREBP is divided by S1P and S2P (Site Protease 1 and Site Protease 2), which are two enzymes activated by SCAP when cholesterol levels are low.

The slotted SREBP then travels to the nucleus, and acts as a transcription factor for binding to the sterol regulatory component (SRE), which stimulates transcription of many genes [(131)]. Among these are low-density lipoprotein (LDL) receptors and HMG-CoA reductase. LDL receptors make circulated LDL scatterers from the bloodstream, while HMG-CoA reduction increases internal cholesterol production.

Cholesterol production can also be stopped when cholesterol levels are high. HMG-CoA reductase contains both the cellular field (responsible for its catalytic function) and the membrane domain. The field of the membrane senses its signs of deterioration. Increased cholesterol (and other sterol) concentrations cause a change in the state of oligomerization in this field, making it more vulnerable to destruction by

proteins. The activity of this enzyme can also be reduced by phosphorylation by AMP activated protein kinase. Since this kinase is activated by cAMP, which is produced when ATP is hydrolyzed by water, it follows that the cholesterol synthesis is stopped when ATP levels are low [(132)].

1.11.2. Cholesterol and prostate health

Attempts to use epidemiological tools to assess any possible association of dietary or circulating cholesterol with the risk of developing clinical prostate diseases faced significant challenges. Another approach is to determine whether long-term treatment with cholesterol-lowering drugs affects the incidence and aggressiveness of prostate tumors. HMG-CoA reductase inhibitors are cholesterol lowering drugs that have been widely used for many years to treat cardiovascular diseases. HMG-CoA reduction stimulates the rate-determining step in the mevalonate pathway, and these factors lower cholesterol by inhibiting its synthesis in the liver and peripheral tissues [(133)].

Potential anti-cancer effectiveness may be lowering cholesterol drugs compared to other methods to lower cholesterol because these factors lower cholesterol in the blood and reduce the synthesis of cholesterol in the peripheral and liver tissues. This may be of great benefit in the case of prostate tumors because the prostate synthesizes cholesterol at a higher rate even than that in the liver [(134)]. It has been shown that HMG-CoAreductase inhibitors exert strong anti-cancer effects in model systems. Studies on cell culture models have indicated that statin drugs can inhibit the growth and movement of cancer cells, induce programmed cell death, and in the prevention of endothelial cell migration and tube

formation, which are properties associated with vascular formation. For example, mycoastatin has been shown to inhibit progression of the cycle cell in human PCA 3 cells by inhibiting independent kinase phosphorylation (CDK) 2 [(135)]. Animal studies have demonstrated that this class of factors has a significant ability to inhibit tumor growth, in vascular vivo and metastatic tumor metastasis. Strong selectivity of tumor cells over normal cells, which are an essential feature of successful cancer treatment [(136)].

Its ability to enhance the effectiveness of conventional chemotherapeutic agents has also been proven. They examined 20,000 patients and compared those taking cholesterol-lowering drugs with those taking other cardiovascular medications from 1983 to 1998 [(137)]. These researchers found a 20% decrease in total cancer incidence in the group of cholesterol-lowering drugs, with the largest decreases in Having prostate and kidney cancer. Patients who completed statin treatment returned to baseline level within 6 months. The results of the National Health and Nutrition Examination Survey showed that statin users have a significantly less prostate-specific antigen (PSA) than non-users (0.90 versus 0.95 ng / ml; p 0.22), especially in men without comorbidities (N 1680; 0.86 vs 0.99 ng / ml; P ¼ 0.02). In men with comorbidities, statin users had a significantly higher non-statistic PSA than non-users (0.91 vs. 0.83 ng / ml; p ¼ 0.14). Men with low cholesterol had a lower PSA (bottom vs. top of the quintile: 0.92 vs. 1.02 ng / ml; p direction ¼ 0.06). This study concluded that statin users and men with low cholesterol may have a lower PSA. If this is the case, the likelihood of detecting prostate cancer without symptoms may be lower today, but it is likely that these

cases will be diagnosed at an advanced stage in the future. Therefore, a PSA bias associated with statin is unlikely to explain the inverse association of advanced prostate cancer [138]. Statin medications (for example, pravastatin, lovastatin, and simvastatin) currently have a clinical history long enough that safety concerns for many of them can be a final evaluation. Since most cholesterol-lowering drugs are now well known to be tolerated by patients, continuous evaluation of these compounds in clinical trials as potential chemical protective agents or as adjuncts to standard therapy is warranted. However, it is not recommended to generalize the effectiveness of statin-fighting anticancer drugs as a group, because different compounds can show markedly different patterns of activity against tumor cells [139].

1.12. Aims of the study

1- Study the relationship between vitamin D and Benign prostatic hyperplasia and the effect of normal levels of vitamin D on Benign prostatic hyperplasia

2- Knowing the relationship between vitamin D and clinical parameters (25-OH total vitamin D, PSA , f PSA , PTH , Testosterone, Calcium Ion , Phosphorus Ion , Serum Zinc, Serum Iron , Cholesterol)

3-Study and knowledge of the relationship between BPH and clinical (PSA , f PSA , PTH , Testosterone, Calcium Ion , Phosphorus Ion , Serum Zinc, Serum Iron , Cholesterol)

4- Study and detect the relationship between clinical parameters among them.

Chapter Two

Materials and Methods

2.1 Materials and methods

2.1.1 : Equipment

In the table (2.1), the machines used in this study were mentioned with the manufacturer and the country of origin

Table 1.1 the machines used in this study

machines	Company	Origin
BA-88A Semi-Auto Chemistry Analyzer	Mindray	China
Centrifuge	cypress diagnostics	Belgium
Deep freeze	Sanyo	Japan
Indiko	Thermo Fisher Scientific	U.S.A
Incubator	cypress diagnostics	Belgium
Maglumi 800	Snibe	China
Micropipettes / pipettes	Gilson	France
Spectrophotometer	Apple PD303	Japan
Vortex	Stuart	U.S.A
Water bath	cypress diagnostics	Belgium

2.1.2 Chemical substances and groups

In the table (2.2) are the chemicals used in the study, manufacturer, and country of origin.

Table 2.2 Materials and chemicals used in the study

Material	Company	Country
Calcium- kit	HUMAN Diagnostics	Germany
Cholesterol- kit	HUMAN Diagnostics	Germany
Iron- kit	HUMAN Diagnostics	Germany
MAGLUMI Vitamin D (CLIA)	Snibe	China
MAGLUMI Total PSA (CLIA)	Snibe	China
MAGLUMI f-PSA (CLIA)	Snibe	China
MAGLUMI Testosterone (CLIA)	Snibe	China
MAGLUMI intact PTH（CLIA）	Snibe	China
Phosphorus- kit	HUMAN Diagnostics	Germany
Zinc- kit	HUMAN Diagnostics	Germany

2.2 Subjects

2.2.1 Patients and Control Groups

The study included a total of 87 males divided into two groups, 25 control groups and 62 patients with benign prostatic hyperplasia. The first group, the control group, was in good health, ranging in age from (50-80) year. The study was conducted at Yarmouk Teaching Hospital(Baghdad) and the study period was from December 2019 to March 2020 Moreover, the history of treatment, modifications and lifestyle were considered.

2.1.1 The collection of Blood Sample

An intravenous blood sample was collected in the morning, total blood (7-8 ml) from each patient and healthy person. This blood was placed in a gel tube gently and then all blood samples were placed in a cold box under a sterile condition and the serum was centrifuged at 5,000 Revolutions Per minute for 10 minutes and the serum was divided into aliquots in Eppendorf tubes. These tubes was stored in the freezer at (-20 ° C) until the levels of cholesterol, phosphorus, calcium, zinc, iron, vitamin D3 level, testosterone concentration, prostate excretion were estimated. , by chemiluminescence immunoassay technologies.

2.3 Methods

2.3.1 Calculation of Body Mass Index (BMI)

The body mass index was calculated by dividing the person's weight (kg) by the square height (m^2). Weight was measured on an electronic

sensor scale, while height was measured in meters using a standard tape measure (140).

BMI = weight (kg) / length^2 (M) ^{2}

The following table shows the standard weight status categories associated with adult BMI ranges [(140)].

Table 2.3: the standard weight status categories associated with adult BMI ranges

BMI (kg /m ^{2})	**Wight status**
< 18.5	Under weight
18.5 to 24.9	Healthy weight
25.0 to 29.9	Over weight
30.0 to 39.9	Obese
> 40	Highly obese

2.3.2 Laboratory investigation

The following tests were performed in all patients as well as in control.

1- Vitamin D_3.

2- Prostatic-specific antigen (PSA)

3- Free prostatic-specific antigen (f PSA)

4- Para thyroid hormone (PTH).

5- Testosterone

6- Calcium Ion

7- Phosphorus Ion

8- Serum Zinc

9- Serum Iron

10-Cholesterole

2.3.2.1 Measurement of vitamin D_3.

Concentration of vitamin D3 was determined by using Maglumi 800 analyzer.

A. Principle of the test

Competitive immunoassay: Use the purified 25-OH Vitamin D antigen to label ABEI, and use 25-OH Vitamin D antibody for the FITC label. The sample, titrator, or control is mixed with the displacement detector, FITC label, and FITC-coated magnetic microbes completely and incubated at 37 ℃, to form antibody complexes of the antigens; after sediments in a magnetic field, pour the supernatant and then a one-time wash cycle. Then add ABEI Label, incubation and washing for the second time, and the antigen sample and ABEI labeled antigen compete to compete with the FITC monoclonal antibody to form antibody complexes. After this, the starting reagents are added and a flashing chemical reaction begins. The light signal is measured by a photomultiplier such as RLU within 3 seconds and is proportional to the 25-OH Vitamin D concentration present in the samples [(141)].

B. KIT COMPONENTS

Material Supplies

Reagent Integral for 100 determinations	
Nano magnetic microbeads: TRIS buffer, 1.2% (W/V), 0.2%NaN3, coated with sheep anti-FITC polyclonal antibody.	2.5ml
Calibrator Low: bovine serum, 0.2%NaN3.	3.0ml
Calibrator High: bovine serum, 0.2%NaN3	3.0ml

Displacing reagent: acidic buffer	6.5ml
FITC label: 25-OH Vitamin D monoclonal antibody labeled FITC contains BSA, 0.2%NaN3.	12.5ml
ABEI label: 25-OH Vitamin D antigen labeled ABEI, contains BSA, 0.2%NaN3	12.5ml
All reagents are provided ready-to-use.	

Reagent Vials in kit box	
Internal Quality Control: containing BSA, 0.2%NaN3. (target value refer to Quality Control Information data sheet)	2.0ml

C. Preparation of the Reagent Integral

We set up the detector before removing the seal, as we moved the necessary gentle and accurate horizontal integration (while avoiding the formation of foam) And we removed the seal and turned the small wheel from the magnetic microbe chamber forward and back, until the color changed to brown. We put the integration in the detector area and leave it for 30 minutes. During this time, the magnetic microbes will automatically turn on and completely re-suspended.

The analyzer automatically calculates the concentration of 25-OH Vitamin D in each sample by means of a titration curve generated by performing a major two-point titration curve procedure. Results are expressed in ng / ml.

D. Normal value

Vitamin D status	25-OH Vitamin D concentration	
	ng/mL	nmol/L
normal	30-100	75-250

2.3.2.2 Measurement of Prostatic-specific antigen (PSA)

Concentration of (PSA) was determined by using Maglumi 800 analyzer.

A. Principle of the test

Immuno-sandwich assay: Use a PSA monoclonal antibody to label ABEI and use another monoclonal antibody to mark nano magnetic beads. The sample, titrator, or control is mixed well with fine nano-magnetic granules and insulator in a cuvette, incubated at 37 ° C and then washed once-cycle. Then add ABEI Label and embrace it to form a sandwich. After the sediments in the magnetic field, absorb the supernatant and then wash the wash cycle for the second time. Next, Starter 1 + 2 substrates are added and a flash chemical reaction begins. The light signal is measured by a photo multiplier such as RLU within 3 seconds and is proportional to the PSA concentration present in the samples.

B. KIT COMPONENTS

Material Supplies

Reagent Integral for 100 determinations	
Nano magnetic micro-beads: micro-beads coated with anti-PSA monoclonal antibody, contains BSA, 0.2%NaN3.	2.5ml

Calibrator Low: bovine serum, 0.2%NaN3.	2.5ml
Calibrator High: bovine serum, 0.2%NaN3	2.5ml
Buffer: contains BSA, 0.2%NaN3	12.5ml
FITC label: 25-OH Vitamin D monoclonal antibody labeled FITC contains BSA, 0.2%NaN3.	12.5ml
ABEI Label: anti-PSA monoclonal antibody labeled ABEI contains BSA, 0.2%NaN3.	22.5ml
Diluent: 0.9% NaCl	25ml
All reagents are provided ready-to-use.	

Reagent Vials in kit box	
Internal Quality Control: containing BSA, 0.2% NaN3. (target value refer to Quality Control Information date sheet)	2.0ml

C. Preparation of the Reagent Integral

We set up the detector before removing the seal, as we moved the necessary gentle and accurate horizontal integration (while avoiding the formation of foam) And we removed the seal and turned the small wheel from the magnetic microbe chamber forward and back, until the color changed to brown. We put the integration in the detector area and leave it for 30 minutes. During this time, the magnetic microbes will automatically turn on and completely re-suspended.

The analyzer automatically calculates the concentration of PSA in each sample by means of a titration curve generated by performing a major two-point titration curve procedure. Results are expressed in ng / ml.

D. Normal value

Male < 4ng/ml.

Female < 0.5ng/ml.

2.3.2.3 Free prostatic-specific antigen (f PSA)

Concentration of (f PSA) was determined by using Maglumi 800 analyzer.

A. Principle of the test

Principle of sandwich immunoassay test; use f-PSA monoclonal antibody to name ABEI and use another monoclonal antibody to paint magnetic microbes. The sample, titrator, or control is mixed with ABEI Label, buffer and magnetic microbes completely and incubated at 37 ° C, to form a sandwich; after sediment in a magnetic field, pour the supernatant and then a one-time wash cycle. After this, the starting reagents are added and a flashing chemical reaction begins. The light signal is measured by a photo multiplier such as RLU within 3 seconds and is proportional to the f-PSA concentration present in the samples [(142)].

B. KIT COMPONENTS

Material Supplies

Reagent Integral for 100 determinations	
Nano magnetic microbeads: coated with anti-f-PSA monoclonal antibody, contains BSA, 0.2%NaN_3.	2.5ml
Calibrator Low: bovine serum, 0.2%NaN_3.	2.5ml
Calibrator High: bovine serum, 0.2%NaN_3	2.5ml
Buffer: contains BSA, 0.2% NaN_3	10.5ml

ABEI Label: anti-f-PSA monoclonal antibody labeled ABEI, contains BSA, 0.2%NaN_3	10.5ml
All reagents are provided ready-to-use.	

Reagent Vials in kit box	
Internal Quality Control: containing BSA, 0.2%NaN_3. (target value refer to Quality Control Information date sheet)	2.0ml

C. Preparation of the Reagent Integral

We set up the detector before removing the seal, as we moved the necessary gentle and accurate horizontal integration (while avoiding the formation of foam!) And we removed the seal and turned the small wheel from the magnetic microbe chamber forward and back, until the color changed to brown. We put the integration in the detector area and leave it for 30 minutes. During this time, the magnetic microbes will automatically turn on and completely re-suspended.

The analyzer automatically calculates the concentration of f-PSA in each sample by means of a titration curve generated by performing a major two-point titration curve procedure. Results are expressed in ng / ml.

D. Normal value

The results of the study in clinical centers with a group of individuals were 95% of the results: male <1.5 ng / ml female <0.1 ng / ml.

2.3.2.4 Parathyroid hormone (PTH).

Concentration of **(**PTH**)** was determined by using Maglumi 800 analyzer.

A. Principle of the test

Sandwich Analysis Use an anti-PTH monoclonal antibody to label ABEI, and use another monoclonal antibody to label FITC. The sample, titrator, or control, ABEI Label, FITC Label and magnetic microbeads coated with anti-FITC was well installed and incubated at 37 ℃, to form a sandwich; after sediments in the magnetic field, pour the supernatant, then a one-time washing cycle. After this, the starting reagents are added and a flashing chemical reaction begins [(143)]. The light signal is measured by an optical multiplier such as RLU within 3 seconds and proportional to the current PTH concentration controlled by the samples.

B. KIT COMPONENTS

Material Supplies

Reagent Integral for 100 determinations	
Nano magnetic microbeads: TRIS buffer, 1.2%(W/V), 0.2%NaN3, coated with sheep anti-PTH polyclonal antibody.	2.5ml
Calibrator low	3.0ml
Calibrator high	3.0ml
ABEI Label: anti-PTH monoclonal antibody labeled ABEI contains BSA, 0.2%NaN3.	12.5ml
All reagents are provided ready-to-use.	

C. Preparation of the Reagent Integral

We set up the detector before removing the seal, as we moved the necessary gentle and accurate horizontal integration (while avoiding the formation of foam!) And we removed the seal and turned the small wheel from the magnetic microbe chamber forward and back, until the color changed to brown. We put the integration in the detector area and leave it for 30 minutes. During this time, the magnetic microbes will automatically turn on and completely re-suspended.The analyzer automatically calculates the concentration of PTH in each sample by means of a titration curve generated by performing a major two-point titration curve procedure. Results are expressed in ng / ml.

D. Normal value

<80pg/ml.

2.3.2.5 Testosterone

Concentration of Testosterone was determined by using Maglumi 800 analyzer.

A. Principle of the test

Competitive immunoassay. The test monoclonal antibody was used to label ABEI, and the purified TEST antigen was used for the FITC label. The sample, titrator, or control is mixed with ABEI Label, displacement detector, FITC label and FITC-coated magnetic microbes completely and incubated at 37 ℃, to form antigen-antibody complexes; after sediments in the magnetic field, pour the supernatant and then wash it [(144)]. After this, the starting reagents are added and a flashing chemical reaction

begins. The light signal is measured by a photo multiplier such as RLU within 3 seconds and is proportional to the test concentration present in the samples.

B. KIT COMPONENTS

Material Supplies

Reagent Integral for 100 determinations	
Nano magnetic microbeads: TRIS buffer, 1.2% (W/V), 0.2%NaN_3, coated with anti-FITC polyclonal antibody	2.5ml
Calibrator Low: bovine serum, 0.2%NaN_3	2.5ml
Calibrator High: bovine serum, 0.2%NaN_3	2.5ml
Displacing Reagent: Tris Buffer containing 0.5% ANS, 0.2%NaN_3.	4.5ml
FITC Label: purified TEST antigen labeled FITC, containing BSA, 0.2%NaN_3.	6.5ml
ABEI Label: anti-TEST monoclonal antibody labeled ABEI, containing BSA, 0.2%NaN_3.	6.5ml
All reagents are provided ready-to-use.	

Reagent Vials in kit box	
Internal Quality Control: containing BSA, 0.2%NaN_3. (target value refer to Quality Control Information date sheet)	2.0ml

C. Preparation of the Reagent Integral

We set up the detector before removing the seal, as we moved the necessary gentle and accurate horizontal integration (while avoiding the formation of foam!) And we removed the seal and turned the small wheel from the magnetic microbe chamber forward and back, until the color changed to brown. We put the integration in the detector area and leave it

for 30 minutes. During this time, the magnetic microbes will automatically turn on and completely re-suspended. The analyzer automatically calculates the concentration of Testosterone in each sample by means of a titration curve generated by performing a major two-point titration curve procedure. Results are expressed in ng / ml.

D. Normal value

Male 2.2-10.5ng/ml

Female<1.0ng/ml

2.3.2.6 Calcium Ion

A. Principle

Calcium ions react with o-cresolphthalein-complexone in an alkaline medium to form a purple complex. The absorbance of this complex is directly proportional to the calcium concentration in the sample [(145)].

B. Kit contents

BUF	100 mol / l Buffer solution	
	Lysine buffer(pH 11.1)	0.2 mol / l
	Sodium azide	0.095 %
RGT	100 ml color reagent	
	8-hydroxyquinoline	14mmol / l
	o-cresphthalein-complexone	0.1 mmol / l
	Hydrochloric acid	40 mmol / l
STD	3 ml standard	
	Calcium(II)	8 mg/dl
	Sodium azide	0.095 %

C. Assay Procedure

To prepare the reagent we add[RGT] to an equal volume of [BUF] as required mix and let stand for 30 minutes at room temperature before use.

Wavelength: 570 nm, Hg578 nm

Light step: 1 cm

Temperature: 20…25°C

Measurement: In front of the reactive blank per series.

Pipetting scheme

Pipette into cuvettes	Reagent blank	Sample or STD
Sample / STD	---	20 µl
Working reagent	1000 µl	1000 µl

Mix and measure the absorbance of the sample ($\triangle A_{Sample}$) and the standard ($\triangle A_{STD}$) against reactive blank within 5 to 30 minutes

Concentration is calculated according to the formula

$$C\ (mg/dl) = \frac{\Delta A\ Sample}{\Delta A\ STD} \times 8$$

D. Normal value

Serum / plasma 8.1 – 10.4 mg/dl or 2.02 – 2.60 mmol / l

2.3.2.7 Measurement of Phosphorus Ion

A. Principle

Phosphate reacts with molybdate in strong acidic medium to form a complex . The absorbance of this complex in the near UV is directly proportional to the phosphate concentration [146].

Reaction principle:

$7H_3PO_4 + 12(Mo_7O_{24})^{6-} + 51\ H^+ \longrightarrow 7[P(Mo_{12}O_{40})]^{3-} + 36H_2O$

B. Kit contents

RGT	Ammoniumhebtamolybdate	0.3 mmol/l
	Sulphuric acid (pH < 1.0)	160 mmol/l
	Detergent	1 %
	Activators and stabilisers	
STD	phosphorus	10 mg/dl or 3.2mmol/l

C. Assay Procedure

Wavelength: 340 nm, Hg 334 nm

Optical path: 1 cm

Temperature: 20…..25 °C

Measurement: against reagent blank ; one reagent blank per series is required

Pipetting scheme

Pipette into cuvettes	Reagent blank	Sample or STD
Sample / STD	---	10 µl
RGT	1000 µl	1000 µl

Mix, incubate at least 1 minute at room temperature. Measure the absorbance of the sample and the STD against the reagent blank within 60 minutes (△A).

Concentration is calculated according to the formula

$$C\ (mg/dl) = \frac{\Delta A\ Sample}{\Delta A\ STD} \times 10$$

D. Normal value

Adults: 2.5 – 5.0 mg/dl

Children: 4.0 – 7.0 mg/dl

2.3.2.8 Measurement of Serum Zinc

A. Principle

Zinc reacts with the chromogen present in the reagent forming acoloured compound which colour intensity is proportional to the zinc concentration present in the sample [(147)].

B. Kit content

Reagent A	Borate buffer	0.37 M pH 8.2
	Saliciladoxime	12.5 mM
	Dimetilgioxime	1.25 mM
	Surfactants and preservatives	
Reagent B	NITRO-PAPS	0.4 mM
Standard	Zinc ion	200 µg/dl
	Stabilizers and preservatives	

C. Assay Procedure

Kind of analysis: End point

Reading time: 5 minutes

Color stability: 30 minutes

Wavelength: 578 nm (520-570)

Temperature: 20-25 °C

Light path: 1 cm

Zero: Blank Reagent

Reagents	Blank	Standard	sample
Work Reagent	1 ml	1ml	1ml
Distilled Water	50 µl	--	--
Standard	--	50 µl	--
sample	--	--	50 µl

Mix and read the absorbance against blank at 578 nm. Color is stable for 30 minutes.

Concentration is calculated according to the formula

$$\text{Zn } \mu\text{g/dl} = \frac{A\ Sample}{A\ Standard} \times 200$$

E. Normal value

70 – 115 **µ**g/dl

2.3.2.9 Measurement of Serum Iron

A. Principle

Iron (III) react with chromazurol B (CAB) and cetyltrimethylammonium-bromide (CTMA) to form a coloured ternary complex with an absorbance maximum at 623 nm. The intensity of the colour produced is directly proportional to the concentration of iron in the sample [148].

B. Kit content

Reagent	CAB	0.18 mmol/l
	CTMA	2.2mmol/l
	Guanidinium chloride	2.6 mol/l
	Sodium acetate buffer (pH 4.7)	45 mmol/l
Standard	Iron (ionized)	100 µg/dl

C. Assay Procedure

Wavelength: 623nm

Optical path: 1 cm

Temperature: 20…25 °C

Measurement: against reagent blank(Rb)

Pipetting scheme

Pipette into cuvettes	Reagent blank	Sample or STD
Sample / STD	---	50 µL
Distilled water	50 µL	---
RGT	1000 µL	1000 µL

Mix well, incubate for 15 minutes at 20…25°C measure the absorbance of the sample($\triangle A_{Sample}$) and the standard (($\triangle A_{standard}$) against the reagent blank within 60 minutes.

Concentration is calculated according to the formula

$$C\ [\mu g/dl] = \frac{A\ Sample}{A\ Standard} \times 100$$

D. Normal value

Male: 59 - 148 µg/dl

Female: 37 – 145 µg/dl

2.3.2.10 Measurement of Serum Cholesterol

A. Principle

Cholesterol is determined after enzymatic hydrolysis and oxidation. the indicator is the quinoneimine formed by the peroxide of hydrogen and 4-aminoantipyrine in the presence of phenol and peroxidase[(149)].

$$\text{Cholesterol esters} + H_2O \xrightarrow{CHE} \text{cholesterol} + \text{fatty acids}$$

$$\text{Cholesterol} + O_2 \xrightarrow{CHO} \text{cholestene-3-one} + H_2O$$

$$2H_2O_2 + \text{4-aminoantipyrine} + \text{phenol} \xrightarrow{POD} \text{quinoneimine} + 4H_2O$$

B. Kit content

Reagent	Phosphate buffer(pH 6.5)	30mmol/l
	4- aminoantipyrine	0.3 mmol/l
	Phenol	5mmol/l
	peroxidase	≥ 5 KU/l
	Cholesterol esterase	≥ 150 U/l
	Cholesterol oxidase	≥ 100 U/l

	Sodium azide	0.05 %
Standard	cholesterol	200mg/dl
	Sodium azide	0.095 %

C. Assay Procedure

Wavelength: 500 nm, Hg 546 nm

Optical path: 1 cm

Temperature: 20…25 °C or 37°C

Measurement: against reagent blank. Only one reagent blank per series is

Required

Pipetting scheme

Pipette into cuvettes	Reagent blank	Sample or STD
Sample / STD	---	10 µl
RGT	1000 µl	1000 µl

Mix, incubate 10 min at20…25 °C or 5 min at 37°C measure the absorbance of the sample /standard against the reagent blank ($\triangle$A) within 60 min.

Concentration is calculated according to the formula

$$C\ [mg/dl] = \frac{A\ Sample}{A\ Standard} \times 200$$

D. Normal value

Adults ≤ 190 mg/dl or 5.0 mmol/l

2.4 Statistical analysis

The data were analyzed using the, Microsoft excel, Minitab v17, and IBM SPSS V26. The results reported in this study were expressed as mean SD. one-way analysis of variance was used to examine the degree of significance between groups, Independent t test, and person correlation were used to examine the relationship between variables. Probability values less than 0.05 were considered significantly different. (Daniel and Cross , 2013).

Chapter three

Results and Discussion

Results and Discussion

3.1 Age and Body mass index

This study includes the effect of vitamin D and its relationship with patients with benign prostatic hyperplasia (BPH) in men over the age of fifty with a measure of some clinical criteria. The study included 87 samples, including 63 patients and 25 controls. The mean age of the patients was (65.16 ± 8.51) and the control group (59.04 ± 4.62). As shown in Figure 3.1.

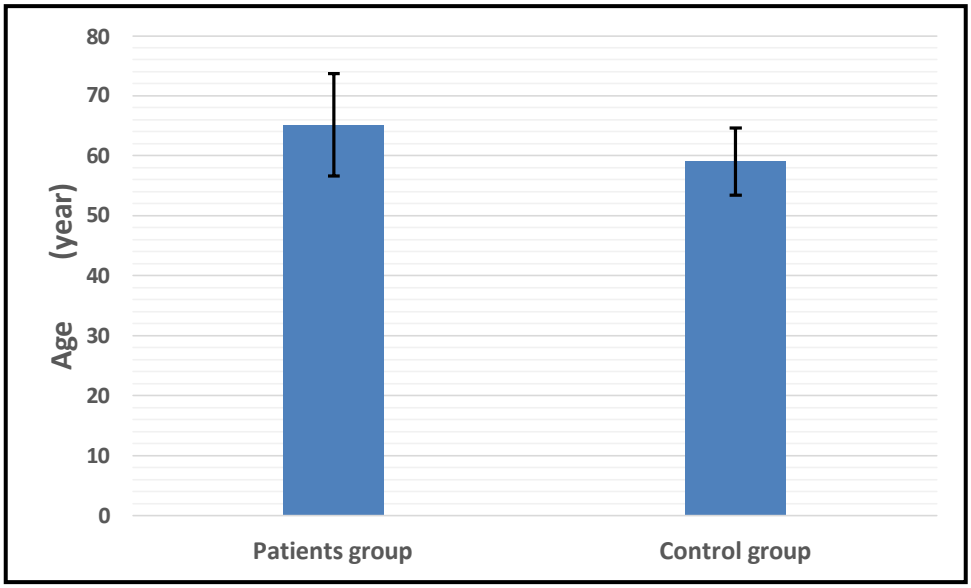

Figure 3.1: Mean Age for BPH patients and controls group

It was observed that the average age value of patients with benign prostatic hyperplasia (65.16 ± 8.51) years was higher than the control group age (59.04 ± 4.06) years (figure 3.1).The result was significant at P≤0.05.table 3.1. As the benign prostatic hyperplasia increases with ageand. these results were somewhat consistent with the previous studies (150).

Table 3-1: correlation and P-value in Age between patient and control group.

Parameters	Patient (N=62)	Control (N=25)	P-value¥
	Mean±SD	Mean±SD	
Age(year)	65.16±8.51	59.04±4.62	0.001 ***

¥: Independent t-test were employed, *, **, * significant (P<0.05), highly significant (P<0.01), and very high significant (P<0.001) respectively**

From the observation of the body mass index BMI, it was found that the mean value for it in the group that included patients with BPH is (26.45±2.83) kg/m^2 compared to the average value for the control group (25.11±2.85) kg/m^2.

Where the results were for patients with BPH (35%) Normal weight (50%) overweight (14%) obese and the results of the control group (68%) Normal weight (24%) overweight (8%) obese as shown in the table (3.1)

Table 3-2 : Body mass index results in the study groups

BMI	patients with BPH	control
Mean ±SD (in Kg/m2)	26.45±2.83	25.11±2.85
Normal (<25)	22(35%)	17(68%)
over weight (25- 29.9)	31(50%)	6(24%)
(Obese >30)	9(14%)	2(8%)

The results showed that there was slight significant relationship between body mass index (BMI) and BPH patients. The percentage of obesity and weight gain in the BPH patients group was close to that of the control group and this result differed with a previous study [(151)]. There was no

significant indication of statistical significance. Our study coincides with a previously conducted study [152] which showed no relationship between BMI and BPH.

3.2 Prostatic-specific antigen (PSA) level in the study group

From our study, It was found that PSA levels in a group of BPH patients (4.06 ± 2.93) ng/ml were higher than that in the control group (0.68±0.39) ng/ml (Figure 3.2.) This results was identical to most previous study [153] and also it was found that the majority of BPH patients had a PSA value for them < 1.4 ng/ml ([154].

The study group was divided into two groups: benign prostatic hyperplasia patients who were diagnosed through the digital rectal examination (DRE) in addition to the accompanying symptoms of a feeling of desire to urinate at night and the slow flow of urine and not complete discharge and these symptoms above for patients were diagnosed by the specialist doctor. The control group had relied on healthy people who had normal vitamin D levels to be examined and made sure they were free of an enlarged prostate, and after the examination it was found that (24%) of them had benign prostatic hyperplasia. Therefore they were excluded as a control group for PSA to obtain accurate values for PSA for healthy people (0.68±0.39) ng/ml Figure 3.2.

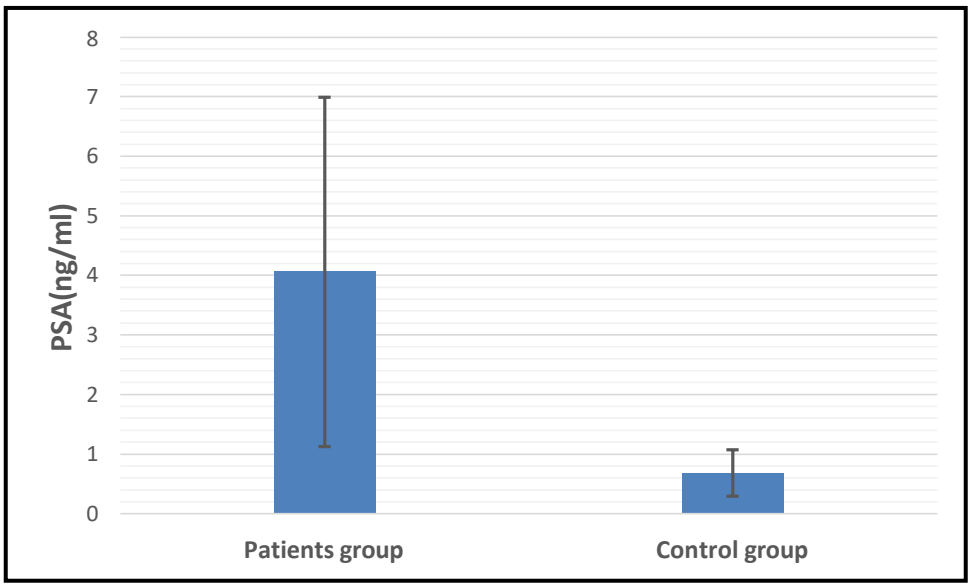

Figure 3.2: Mean PSA for BPH patients and controls

We had a statistically significant relationship between PSA levels in the control group and the patient group, Table (3.3)

Table 3-3: Correlation and P-value in PSA between patient and control group.

Parameters	Patient (N=62)	Control (N=25)	P-value¥
	Mean±SD	Mean±SD	
PSA(ng/mL)	4.06±2.93	0.68±0.39	0.001 ***

¥: Independent t-test were employed, *, **, * significant (P<0.05), highly significant (P<0.01), and very high significant (P<0.001) respectively**

3.3 Free/total PSA ratio level in the study group

In this study, we measure the f PSA was measured and then extracted the ratio of free prostate to the total was calculated. and It is one of the tests that diagnosing benign prostatic hyperplasia and differentiate between it and prostate cancer[(155)], where the PSA value is considered to be (4-10) ng/mL in the area where the person may have benign prostatic hyperplasia or cancer Prostate. This is very helpful in abstaining from

resorting to prostate biopsy. Samples that were diagnosed as prostate cancer and not benign prostatic enlargement were excluded and only three samples were among the patient group. Mean value was obtained for the study group(34.38±13.2) Based on free: total PSA ratio: Probability of prostate cancer table (3.4)

Table 3-4 : Based on FREE: Total PSA Ratio: Probability of prostate cancer

Free:total PSA ratio	50-59 years	60-69 years	70 years and older
< or =10	49%	58%	65%
11-18	27%	34%	41%
19-25	18%	24%	30%
>25	9%	12%	16%

3.4 Parathyroid hormone level (PTH).

The results of PTH levels were 89.29±25.26 pg /ml for patients with benign prostatic hyperplasia while it was 55.04±17.56 pg /ml ,for the controls group.

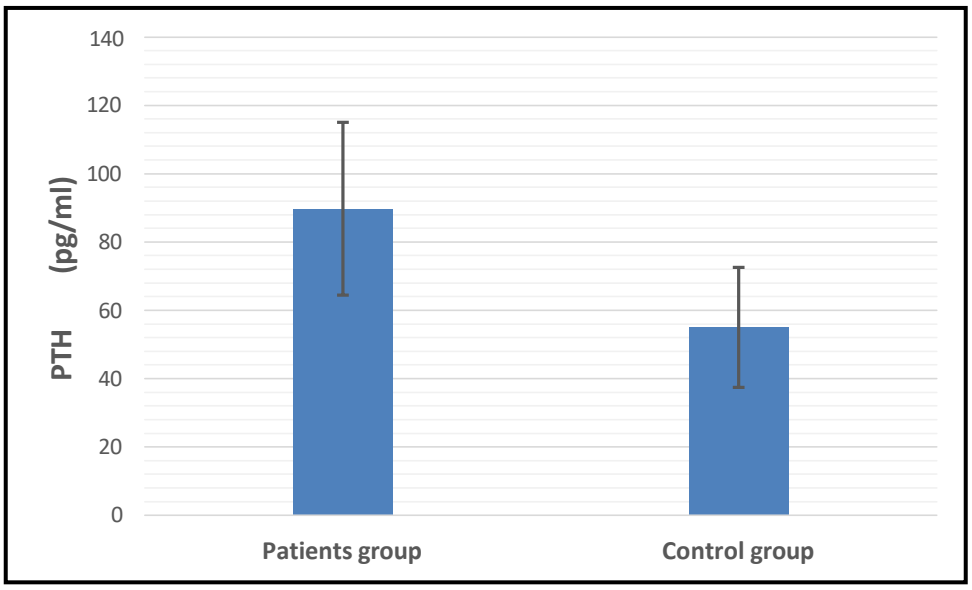

Figure 3.3: Mean PTH level for BPH patients and controls

The levels of PTH in BPH patients were significantly higher compared to controls group. Table (3.5). This result is in agreement with a previous study that showed a relationship between levels of BPH and levels of the parathyroid hormone [(156)]. And others have shown a relationship between prostate diseases and its disorders with higher levels of PTH [(157)], while others have shown no relationship or statistical significance for the association of benign prostatic hyperplasia with PTH [(158)].

Table 3-5:Correlation and P-value in PTH between patient and control group.

Parameters	Patient (N=62)	Control (N=25)	P-value ¥
	Mean±SD	Mean±SD	
PTH (pg/ml)	89.75±25.26	55.04±17.56	0.019 *

¥: Independent t-test were employed, *, **, * significant (P<0.05), highly significant (P<0.01), and very high significant (P<0.001) respectively**

3.5 Testosterone level

The levels of testosterone for patients with benign prostatic hyperplasia were (4.9±1.62)ng/ml, whereas the values for the control group were (4.27±1.88) ng/ml figure 3.4

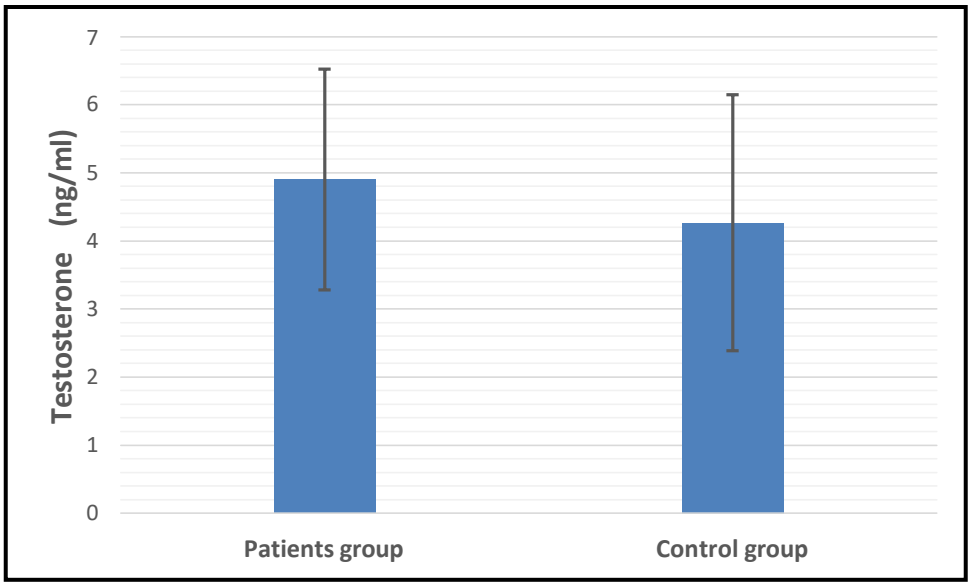

Figure 3.4: Mean Testosterone level for BPH patients and controls

There was no significant difference is observed between testosterone levels in the benign prostatic hyperplasia group and the control group, as the results in both groups was among the normal values. This was consistent with the previous study with BPH [(159)]. While other studies high levels of testosterone [(160)], in patients with benign prostatic hyperplasia. Another study showed that testosterone replacement therapy (TRT) does not show any negative effect on enlarged prostate, however sometimes shows an improvement in its resulting symptoms known as LUTS [(161)].

3.6 Calcium Ion levels

the calcium values were 9.32±0.48mg/dl in patients with benign prostatic hyperplasia and were 9.2±0.26 mg/dl in the controls group figure 3.5

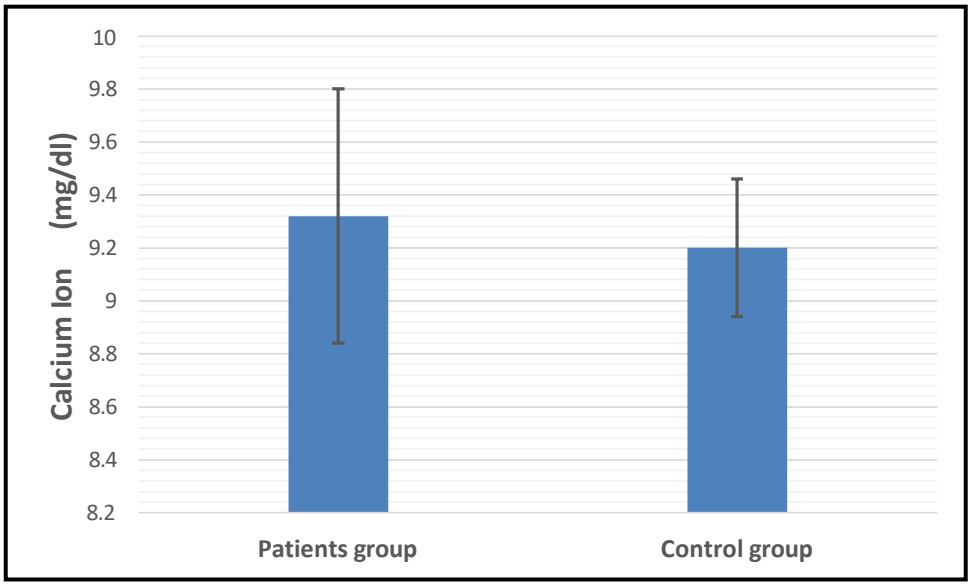

Figure 3.5: Mean Calcium Ion level for BPH patients and controls

The results showed no difference in the results of the blood calcium level of BPH patients and controls group. is compatible with another study that showed that the level of calcium is normal in BPH patients compared to prostate cancer patients [(162)].

3.7 Phosphorus Ion level

the phosphorus values for patients suffering from benign prostatic hyperplasia were 3.82±0.89 mg/dl while the phosphorus values were in the control group 3.85±0.86 mg/dl figure 3.6

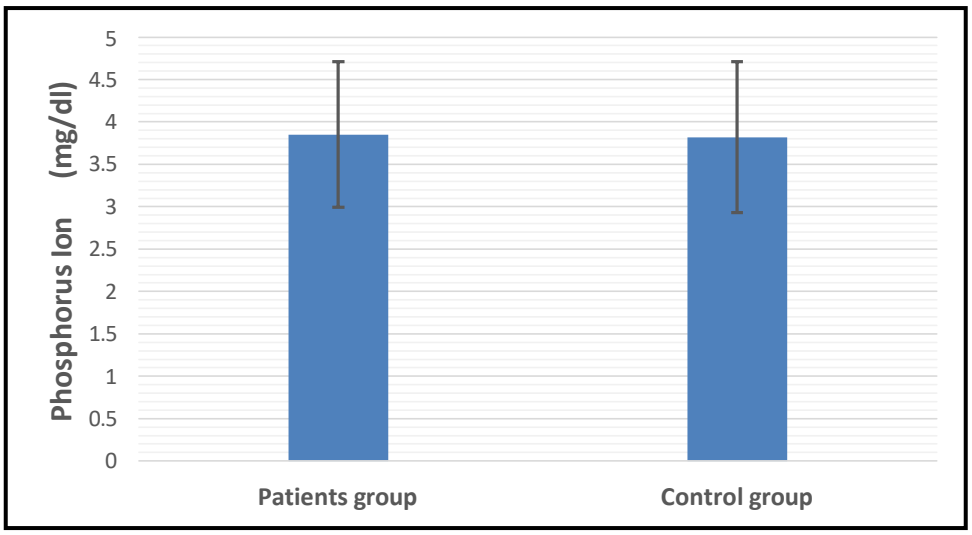

Figure 3.6: Mean Phosphorus level for BPH patients and controls

It emerged that there is no relationship between the level of phosphorous in the blood and BPH,

3.8 Serum Zinc level

the average zinc value in patients with BPH was 98.30±8.64 µg/dl While it was 105.24±7.15 µg/dl in the control group figure 3.7

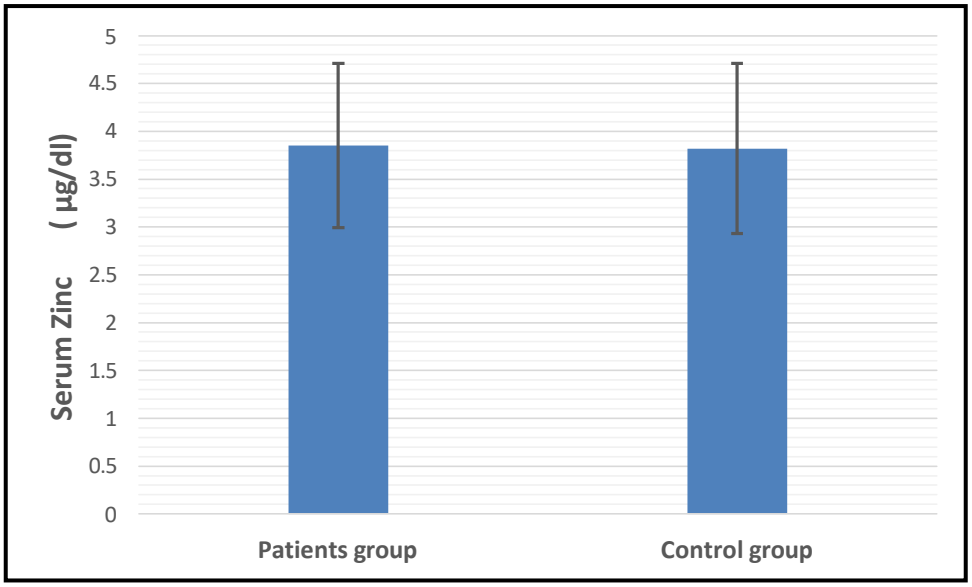

Figure 3.7: Mean Serum Zinc level for BPH patients and controls

The results of zinc tests showed a relationship between zinc levels and benign prostatic hyperplasia (BPH), as the average zinc value in BPH patients 98.30±8.64 mg/dl was lower than the average zinc levels in the control group 105.24±7.15 mg/dl table (3.6), and this result is in agreement with a previous study [163].

Table 3-6: correlation and P-value in Zinc between patient and control group.

Parameters	Patient (N=62)	Control (N=25)	P-value¥
	Mean±SD	Mean±SD	
Zinc(µg/dl)	98.30±8.64	105.24±7.15	0.002 ***

¥: Independent t-test were employed, *, **, * significant (P<0.05), highly significant (P<0.01), and very high significant (P<0.001) respectively**

Zinc is known to accumulate in soft tissues, including prostate cells, and in these cells it inhibits citrate oxidation as well as inhibits the growth and proliferation of prostate cells [164], thus reducing prostate enlargement. zinc levels was only examined in the blood, and here we recommend other research based on examining zinc in prostate tissue and comparing it with zinc levels in serum and urine to reach more comprehensive results.

3.9 Serum Iron levels

the results of the mean value of total iron in serum in the group of BPH patients 96.69±28.40 mg/dl and the mean value of total iron in the serum of the control group 115.73±31.35 mg/dl figure 3.8

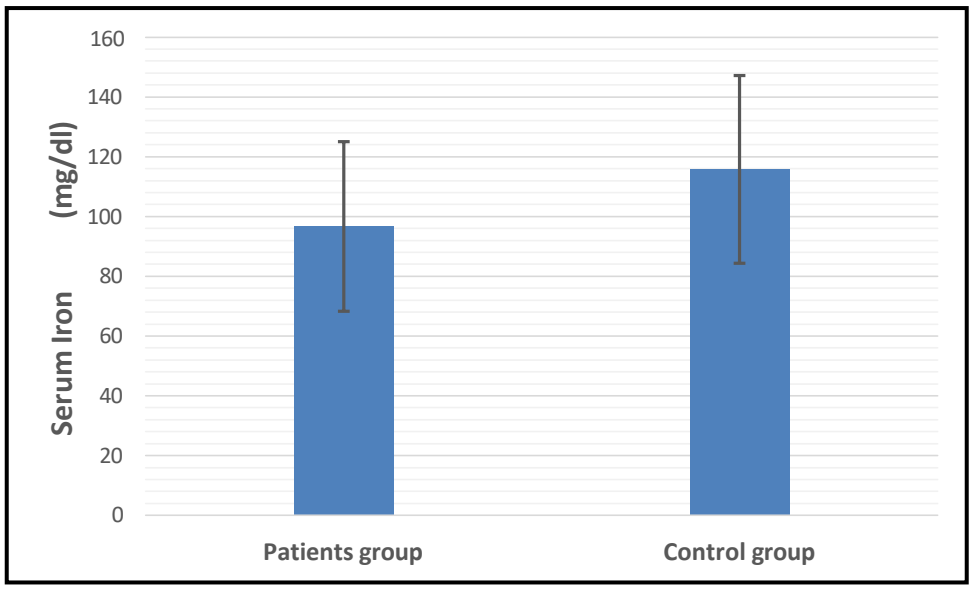

Figure 3.8: Mean Serum Iron level for BPH patients and controls

It was noted a relationship between BPH and the level of iron in the serum, as iron levels were higher in the control group 115.73±31.35 mg/dl compared to patient group 96.69±28.40 mg/dl This result does not agree with a previous study [165] It was showed a positive correlation between BPH and the iron level in the blood.

3.10 Cholesterol levels

the results of the mean value of the cholesterol level in the blood in patients with BPH were 163.64±30.63 mg/dl While, mean value of the cholesterol level in the control group 151.48±22.26 mg/dl figure 3.9

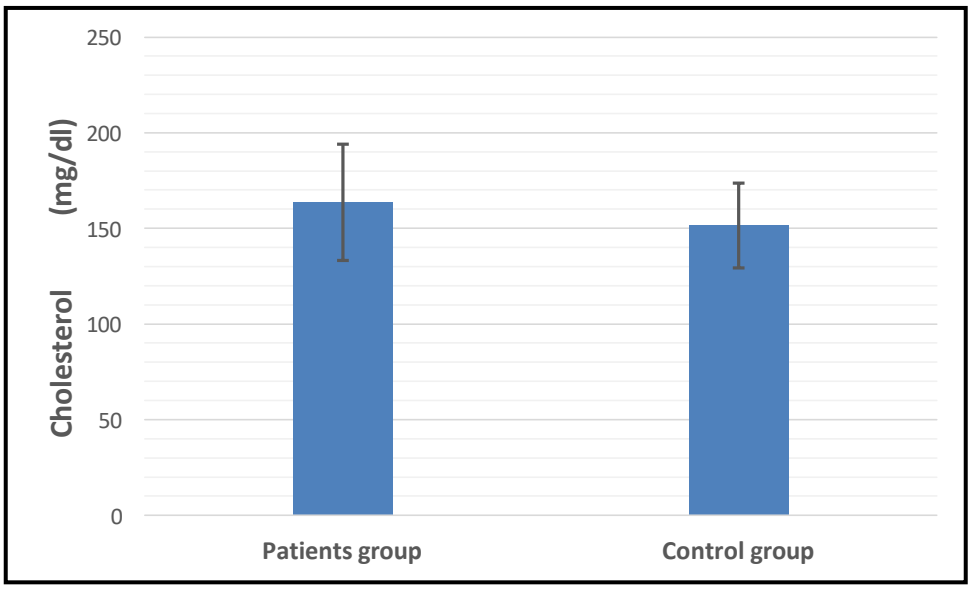

Figure 3.9: Mean Cholesterol level for BPH patients and controls

It was appeared that there is a relationship between BPH and the level of blood cholesterol, as the cholesterol levels in BPH patients were higher than the cholesterol levels in the control group. The increase in cholesterol levels leads to an increase in the likelihood of prostate cells proliferation, which in turn increases the size of the prostate [(166)].

3.11 vitamin D_3 levels

In our study, the focus of our study was on vitamin D level and its relationship to BPH. The study group was divided into two groups, the first group is the group of patients with benign prostatic hyperplasia who were diagnosed by the methods mentioned in the introduction. And this group, we examined the average value of vitamin D3 for them 18.94 ± 6.64 and the second group is the group of men who have normal levels of vitamin and their number (N = 33) were performed the necessary tests for them in order to ensure that they suffer from benign prostatic hyperplasia or not. After examination, it was found that (24%) had an enlarged

prostate with normal levels of vitamin D3 and their number was (N = 8). In this case, we excluded subjects with BPH with normal levels of Vitamin D from the control group. The percentage of people with BPH with normal levels of Vitamin D was (24%) mean ± SD (36.90 ± 4.01) The percentage of healthy people without BPH in the control group (76%)(N=25), mean ± SD (38.89 ± 4.89) Table (3.7)

Table 3-7: Results and ratio of BPH with normal levels of Vitamin D.

	Men with BPH with normal levels of vitamin D (N=8)	**Healthy men without BPH with normal levels of Vitamin D.(N=25)**
Mean ±SD	36.90± 4.01	38.89± 4.89
Percentage	24%	76%

It is evident from the above table that the largest percentage of people with normal levels of Vitamin D did not suffer from BPH. To compare the control group with the patient group, we will exclude people who have BPH with normal levels of Vitamin D and limit it to healthy people from the control group only. And from a comparison of the results of a group of patients whose vitamin D levels were Mean ±SD (18.94± 6.64) with a control group of healthy people who had vitamin D levels Mean ±SD (38.89± 4.89). figure 3.10

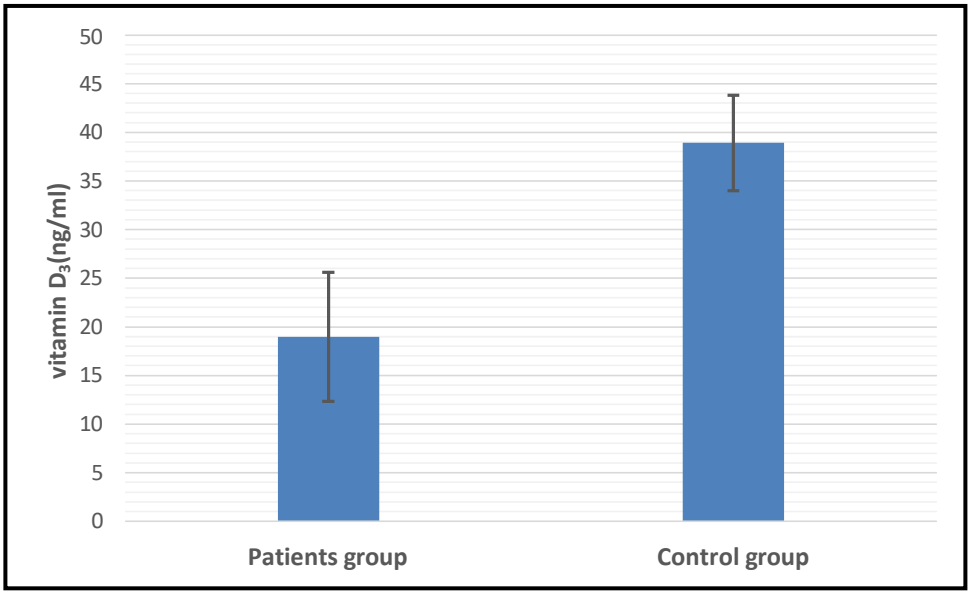

Figure 3.10: Mean vitamin D_3 levels for BPH patients and controls without BPH

It was noted that the values of vitamin D levels in benign prostatic hyperplasia patients (18.94± 6.64)ng/ml were much lower than the control group (38.89± 4.89)ng/ml (P<0.001). (Table 3.8)

Table 3-8: The correlation between the vitamin in a group of benign prostatic hyperplasia patients and a control group of healthy subjects

Parameters	Patient (N=62)	Control (N=25)	P-value¥
	Mean±SD	Mean±SD	
Vitamin D_3(ng/ml)	18.94±6.64	38.90±4.89	0.001 ***

¥: Independent t-test were employed, *, **, * significant (P<0.05), highly significant (P<0.01), and very high significant (P<0.001) respectively**

3.12 The correlation between vitamin D_3 levels and clinical parameters in the study groups

clinical parameters	25-OH total vitamin D			
	BPH patients		Control group	
	R	P	R	P
Age (years)	-0.13	0.303	0.27	0.189
BMI (Kg/m^2)	-0.14	0.291	-0.15	0.481
PSA	-0.32*	0.011	0.12	0.570
f PSA	0.08	0.527	0.41	0.042
f/Total PSA ratio	0.12	0.346	0.23	0.264
PTH	-0.14	0.284	0.04	0.859
Testosterone	0.09	0.486	0.31	0.126
Zinc	-0.19	0.270	0.26	0.204
Iron	0.07	0.569	0.32	0.113
Calcium (mg/dl)	0.01	0.931	0.37	0.065
Phosphorus(mg/dl)	-0.10	0.446	-0.08	0.689
Cholesterol(mg/dl)	0.05	0.689	-0.11	0.592

In a group of BPH patients, there was a significant clear negative relationship between the levels of vitamin D3 and the level of PSA ($p = 0.011$) this result was consistent with another study [167] .In the same context, another study showed no relationship between vitamin D levels and PSA levels [168], Figure 3.11.

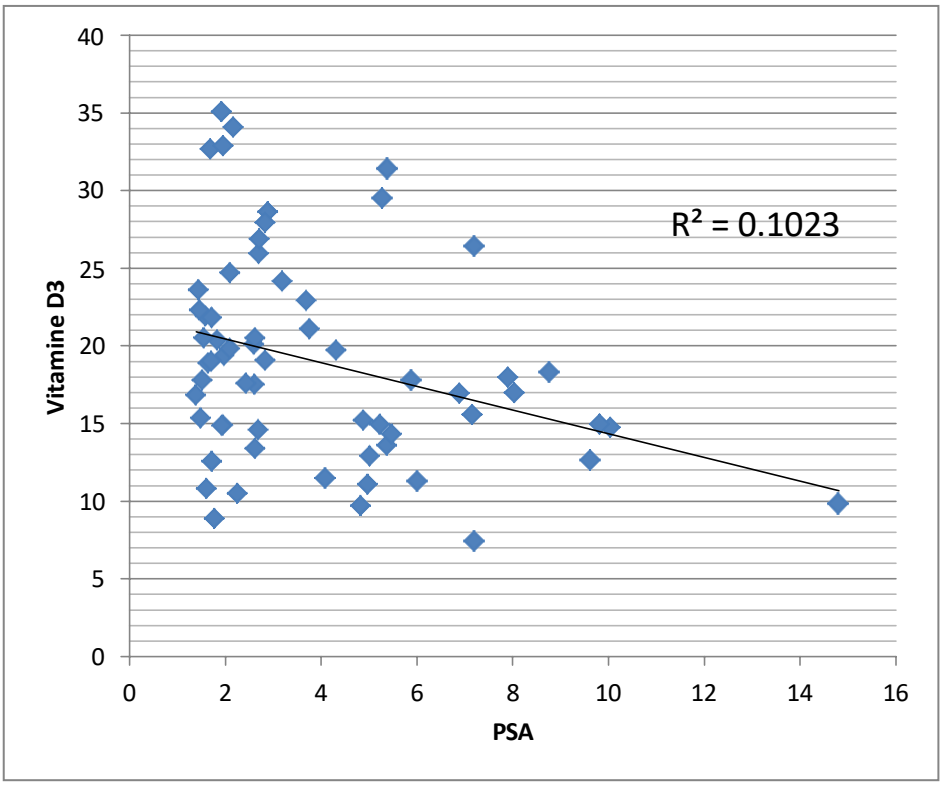

Figure 3.11: Scatter chart showing the significant negative correlation between vitamin D_3 and PSA in patient with BPH under study.

The negative correlation between vitamin D level and PSA supports our study in the relationship of vitamin D to benign prostatic hyperplasia, as an increase in PSA levels is an indicator to presence of prostate enlargement, as previous studies have shown a positive correlation between PSA level and prostate size [(169)].

Our study also showed that there was no significant relationship between each of the parathairoid hormone levels, calcium, phosphorous and vitamin D in the study group, and this result is consistent with the exception that there are other diseases that may affect vitamin D levels[(170)].

3.13 Correlation between clinical biochemistry parameters for the patient group

Through the results of our study, it appears that there is highly significant positive correlation in BPH patients between free PSA and age.(r=0.37) at P<0.01 . Figure 3.12 . The results obtained in this study are in agreement with a previous study on a group of Japanese men [171].

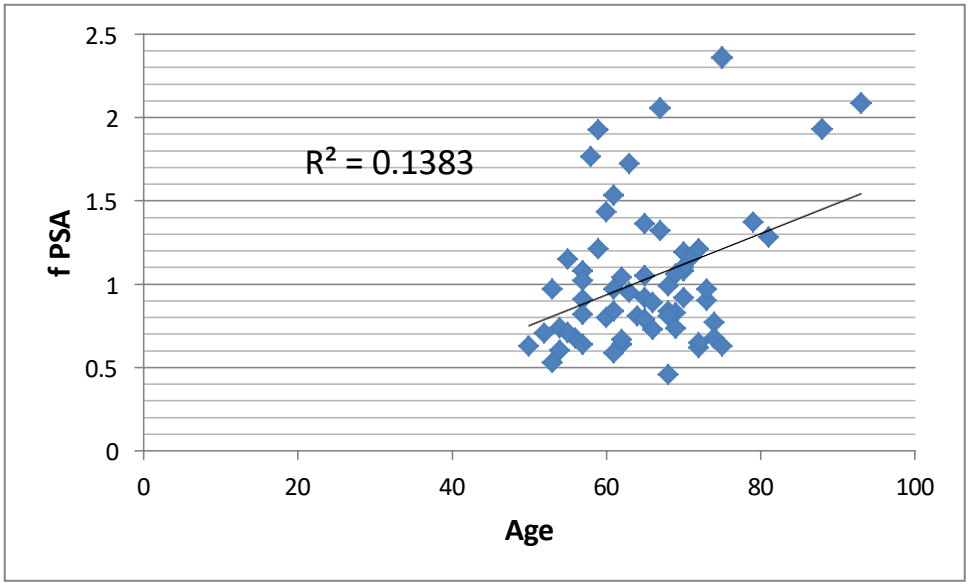

Figure 3.12: Scatter chart showing the highly significant positive correlation between f PSA and Age at P≤0.01 in patient with BPH under study.

In our study, we also found a statistically highly significant negative correlation between serum iron levels and age in patients with BPH. (r= -0.33) at P<0.01 Figure 3.13 . Our study agreed with a previous study [172].

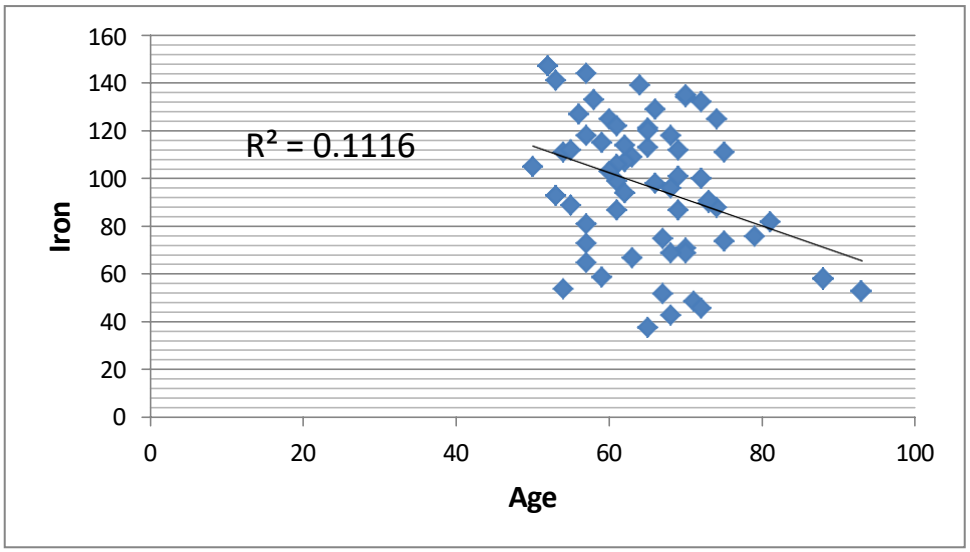

Figure 3.13: Scatter chart showing the highly significant negative correlation between serum iron levels and Age at P≤0.01 in patient with BPH under study.

The results of the study revealed a significant negative correlation between testosterone levels and BMI in BPH patients. (r= -0.31) at P<0.05. Figure 3.14. Our study concurs with a previous study that conducted to assess impotence and the relationship of testosterone to body mass index [(173)].

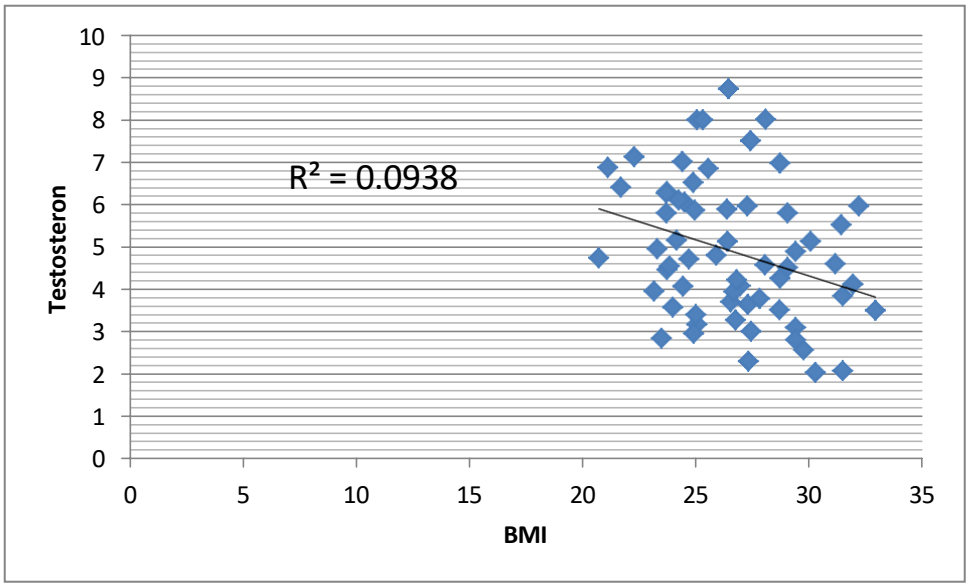

Figure 3.14: Scatter chart showing the significant negative correlation between testosterone levels and BMI at P≤0.01 in patient with BPH under study.

the results also showed significant negative correlation between serum zinc levels and BMI in BPH patients. (r = - 0.26) at P<0.05. Figure 3.15 our study results are consistent with previous study [174] [175].

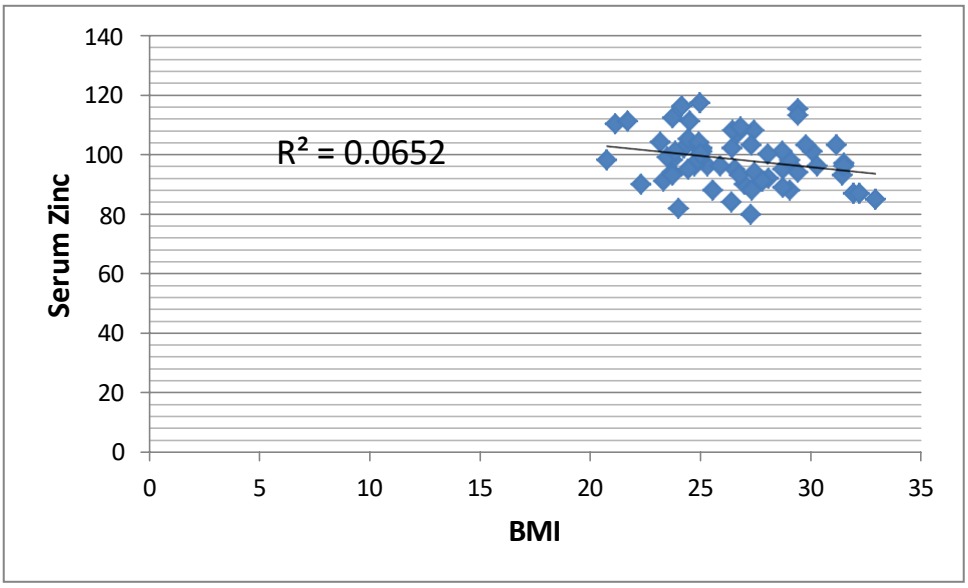

Figure 3.15: Scatter chart showing the significant negative correlation between Serum Zinc levels and BMI at P≤0.01 in patient with BPH under study.

a very high significant negative correlation was observed between free PSA and free to total PSA ratio in BPH patients. (r = - 0.56) at P<0.001. Figure 3.16 .This finding is very important for distinguishing between benign and malignant enlargement of the prostate and reducing prostate biopsy as much as possible which is bothersome to patients. Our study results are consistent and supportive of previous studies [176].

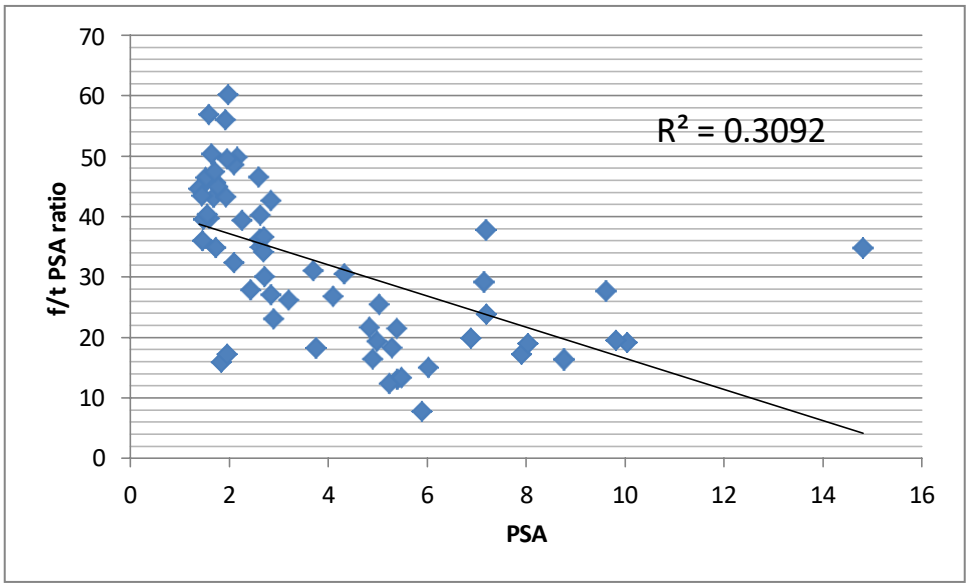

Figure 3.16: Scatter chart showing the very highly significant negative correlation between PSA levels and f/t PSA at P≤0.001 in patient with BPH under study.

It also found a significant negative correlation between testosterone level and parathyroid hormone levels in BPH patients with)r = -0.30) at P<0.05 Figure 3.17

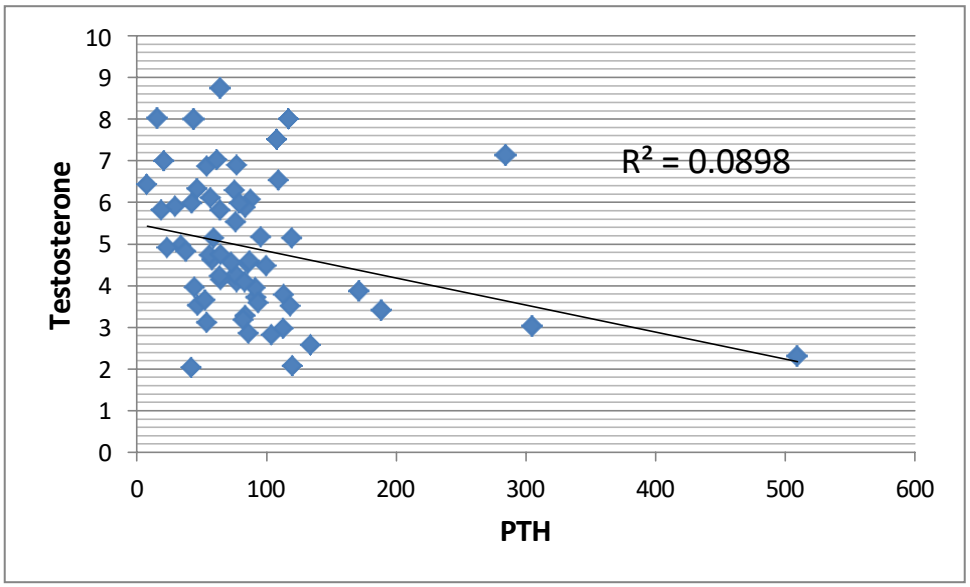

Figure 3.17: Scatter chart showing the significant negative correlation between testosterone levels and parathyroid hormone levels at P≤0.05 in patient with BPH under study.

A highly significant positive correlation was found between PSA levels and parathyroid hormone levels in BPH patients with)r = 0.38) at P<0.01 Figure 3.18 The results of our study are in agreement with a study conducted previously on the same age group[177].

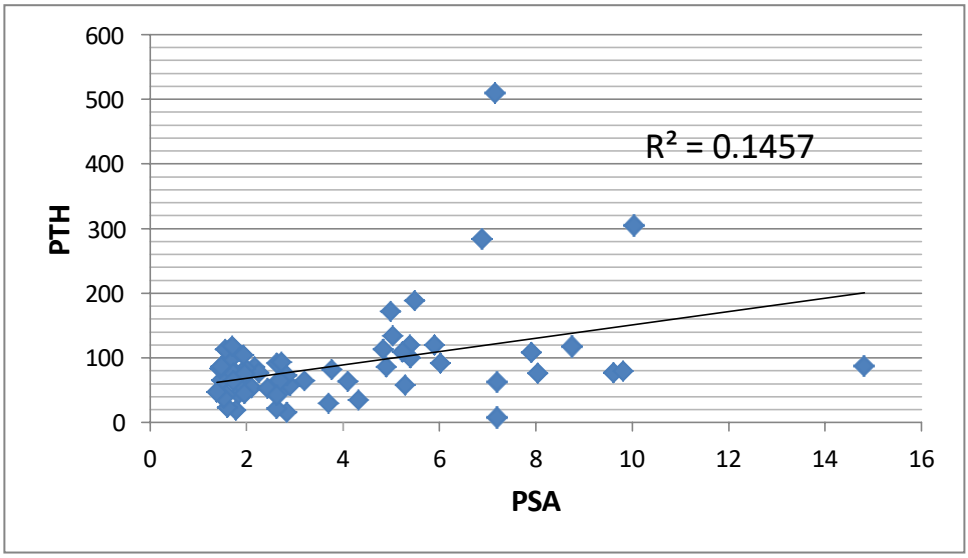

Figure 3.18: Scatter chart showing the highly significant positive correlation between PSA levels and parathyroid hormone levels at P≤0.01 in patient with BPH under study.

There was a very high significant negative correlation between the level of calcium in the blood and the level of testosterone in the BPH patients.)r = -0.41) at P<0.001 Figure 3.19. The results of our study are in agreement with a previous study that showed the inverse relationship between serum calcium levels and sex hormones, including testosterone, and the negative effects of this relationship on prostate health [178].

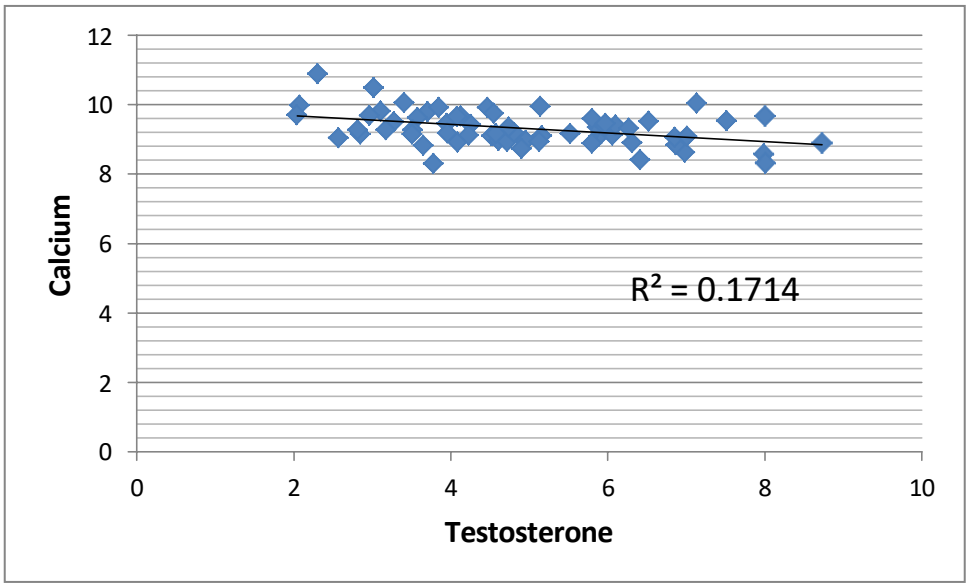

Figure 3.19: Scatter chart showing the highly significant negative correlation between calcium levels and testosterone levels at P≤0.01 in patient with BPH under study.

Zinc levels and their inverse relationship with BMI are still somewhat poorly understood, but there are a number of explanations that could lead to the mechanism through which this relationship can be understood, as weight gain leads to the synthesis of glucocorticoids, which in turn stimulates expression of genes and vectors Zinc through adipocytes, which reduces concentrations in the plasma or serum. Obesity can also lead to oxidative stress disorders that lead to an imbalance of free radicals and antioxidants, as zinc is a component of many antioxidant enzymes [(179)].

There are several explanations for how vitamin D can prevent prostate enlargement, as vitamin D may partially interfere with growth factor (KGF). KGF inhibits apoptosis and stimulates prostate cell proliferation. This contrasts with vitamin D which reduces growth factor. Thus its activity restores the programmed death of prostate cells [(180)].

Conclusions and Recommendations

Conclusions

1- People with normal levels of Vitamin D were less likely to develop BPH. This confirms the direct effect of normal levels of Vitamin D on maintaining prostate health.

2- The presence of a negative relationship between vitamin D and PSA levels supports the direct effect of vitamin D on prostate health and protection from inflation, since PSA levels increase in the case of benign enlargement and other prostate disorders.

3- PSA levels in BPH patients were higher than 1.4 ng / ml and this in turn could be considered a primary diagnostic indicator for BPH.

3- Zinc levels were higher in healthy people than in sick people, and this leads to the fact that maintaining zinc levels has an effect on prostate health.

Recommendations.

1- A histological study and long-term follow-up should be performed for the patients under study, to understand the mechanism by which vitamin D can reduce prostate enlargement.

2- Study other types of trace elements such as copper, cadmium, cobalt, and nickel and their relationship to benign prostatic hyperplasia

3- Study of Prostate membrane-specific antigen (PSMA) and its relationship to benign prostatic hyperplasia.

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Appendixes:

Appendix (1). Questionnaire

Name		Age (years)	
Contact		Address	
Wight (Kg)		Alcoholic	
Height (m)		Smoking	
BMI			
MEDICAL HISTORY			
Prostate diseases			
Diabetic			
Renal diseases			
Other diseases			
Treatments & drugs			
Surgical operations			
Family history of the disease			
Others			

Appendix (2) Correlation coefficient (r) for the patient group

	Age	BMI	PSA	fPSA	f / t PSA ratio	Vit_D3	PTH	Testosterone	Calcium	phosphorus	Zinc	cholesterol
BMI												
PSA												
fPSA	**0.37****											
f / t PSA ratio			**-0.56*****	**-0.31***								
Vit_D3			**-0.32***									
PTH			**0.38****									
Testosterone		**-0.31***					**-0.30***					
Calcium								**-0.41*****				
phosphorus												
Zinc		**-0.26***										
cholesterol												
Iron	**-0.33****								**-0.27***	**0.31***		**0.27***

***, **, *** significant (P<0.05), highly significant (P<0.01), and very high significant (P<0.001) respectively**

الخالصة:-

أثجَزَذ انذساسخ ال طجّخُ انحذُثَخُ أُ رضخٌ انجشُسزبد ع شبئ ع ح ٍَ
انحَََذ ٍش نََََب ُق
ش

َظف اشجبه انزُِ رزشأح أعَب ُِْ ثِ ُاحِذ ُخَسٍِ ُسزٌِ عب ٍَب ، ُرزُذ ٍِزّ انسجخ إنّ

٪٩٠ ف اشجبه فق سِ َُثِ عب ٍَب، ثِنّ أُ ثَ َ ٍس ٍجّجَبد رؤ ٍِدُ إنّ رَ ضغ ٍُِ غُذح
َال خ

انجشُسزبد, ُئ رزطو اغيت انذساسبد انعيَخ انّ ٍسججبد ُاضحخ ٍُن اعزَبدِب َسجبد

سٌّخ نزضخُ انجشُسزبد انحََذ ، ٍُِِ ٍِْب جبءد ٍِزّ انذساسخ نزززٌِ ٍِ ٍِذَ رأثَّش نََََب ٍِِ
)د(

عٍّ رض خٌ انجشُسزبد ٍِ عزٍِّ ، ُزا أجشِّ دساسخٍ ٍَذاّخٍ شٍََ ٍََد انحَح
)عََخ)سجعََب ُُنََبََ ٍٍَِ عََُخ(

ٍِقسَخ إنّ ٍِجعزٍِ انجَعخ االُنّ ض ََذ خَسخً ُعششٍِ شخ ظ ٍَُِ انجَعخ

انضبثطخ انزِ رشَو االشخبص االط حبء انزٍِ ال ُعبٍُ ٍِ رضخٌ انجشُسزبد انحََذ ، أ ٍب

انجَعخ انثَّخ فحيغ عذد أفشادِب اثٍِ ُسزٍِ شخ ظ ٍٍِِ ٍِجعخ االشخبص انزٍِ ُعبٍُ

ٍِ رضخٌ انجشُسزبد انحََذ ، عٍِ ٍََب أ ُ انذساسخ أُج ٍِِشَذ نِ ٍِسزشفِ انشٍَِك انزعٍََِ
)ثغذاد(

ُازذ انذساسخ مبُ أأله ٩٩ ٠٠ إنّ آراس ٩٩٩٩.

رَجٍِ ُعذٍَ رشخّض نََبٍََِ)د(نِ أنشاد انَجٍََعزٍِ أ ُ أالشخبص انزٍُِ ٍُزٍَُِِ ٍِسزٍَُبد

ٍُِخفضخ فٍَزبٍَِ)د(مبّ أمثش عشضخ بالطبثخ ثزضخٌ انجشُسزبد انحََذ ، أ ٍب االشخبص

انزٍِ ٍُذٍٍُِ ٍُسزٌبد طجّعَخ ٍِزا انَزبٍِ ٍِِ انَخ ُفَيب ع ٍِّّ ٍََخ انذساسخ فقذ ُجذ
انعََشٍَخ

انجبحث أ) ٧٦ ٪ (ٍٍٍُِ ال ُعبٍُ ٍِشنالد رضخٌ انجشُسزبد انحََذ.

ُثذساسخ انزغّشاد اسشٍّخ االُخشَ ُجذّب عالقخ سيجّخ ثٍِ ٍِسزٌّبد فزبٍِ)د(

ٍٍُِسزٌبد ٍِسزضذ انجشُسزبد انٍع ، ٍُِزّ انعالقخ ثٍٍُِّب رذعُ عالقخ فزبٍِ)د(ُرأثّش ف

انحٍِّ ٍِ خٌ ، إر رشفع ٍِسزٌبد ٍِسزضذ انجشُسزبد انٍع ف حبنخ انزضخٌ، مَب
انزض

أظِشد انزبئج ُجد عالقخ سيجّخ ثٍِ ٍِسزٌّ ُسجخ ٍِسزضذ انجشُسزبد انحش إنّ انني) f /t

PSA ratio (ٍٍُِسزضذ انجشُسزبد انٍع)PSA(، ٍُِزّ انعالقخ ثٍٍُِّب ٍٍِِخ جذا ثٌطفب

إحدّ اىعاٍيبد األ ُىَخ ىيش ع اىزَّْ ثِ اأٍسأ اىحَّذح ُاىخجّثخ ، ُىحع أ ضا أ ُ ٍ َّق خ

ٍسزضذ اىجشَسزبد اىِّ ف ٍِشضٌ رضخٌّ اىجشَسزبرب اىحَّذ مبّذ أمجش ٍِِ **١.٠**

ٍّبغشاً/ٍيِيّزش ُِّز ثذُىب ُىََِ أُ رسزخذً مذاىخ رشخّظّخ أَّخ ىزضخٌّ اىجشَسزبد

اىحَّذ .

أظٍشد ًَزبئج انذساسخ ًُجد فشُق ٍغُْخ ثٍِ ٍجُّعخ انَشضّ انزًٍِ ُْعبًُّ ٍِ

رضخٌُّ ابجشُسزبد ابحَّذ ًٍُجُّعخ األشخبص األ طجــء ف مو ٍِ (vitamin D_3, PSA,

PTH ,Serum Zinc, Age) ، ف حٍَِ ئٌ رنِ ٍَْبك فشُق ٍغُْخ ثٍِ ابجَعزٍّ ف مٍّ

. (BMI ,Testosterone, Calcium Ion , Phosphorus Ion, Serum Iron ٍٍ

جوهريح العراق

وزارج التعلين العالي والثحث العلوي جاهعح

االنثار- كليح العلوم

قطن الكيوياء

عالقح فيتاهين D_3 هع تعض الوتغيراخ الكيوحييح في هرضى تضخن الثروضتاخ الحويذ

رضالح

هقذهح الى هجلص كليح العلوم - جاهعح االنثار كجسء هن

هتطلثاخ نيل شهادج الواجطتير في الكيوياء هن قثل

الطالثة

دمحم زكي طه العاني

تكالريش كيوياء 3122-3123

اشراف

أ.م.د : حويذ حطين علي

2113 ب . هـ 3131 ب . م