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THE PHENOMENON OF THE PREVALENCE OF AN INCREASE IN THE LEVEL OF PROSTATE-SPECIFIC ANTIGENS (TOTAL AND FREE) FOR PATIENTS OVER 40 YEARS OLD WHO VISIT A TEACHING HOSPITAL IN IRAQ

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IBRAHIM NAYYEF IBRAHIM IBRAHIM

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By Ibrahim Nayyef Ibrahim IBRAHIM

November 2022

We certify that we have read this thesis and that in our opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Science

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Ibrahim Nayyef Ibrahim IBRAHIM

ABSTRACT

THE PHENOMENON OF THE PREVALENCE OF AN INCREASE IN THE LEVEL OF PROSTATE-SPECIFIC ANTIGENS (TOTAL AND FREE) FOR PATIENTS OVER 40 YEARS OLD WHO VISIT A TEACHING HOSPITAL IN IRAQ

Ibrahim Nayyef Ibrahim IBRAHIM

Master of Science in Chemistry

Advisor: Assoc. Prof. Dr. Şevki ADEM

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Prostate cancer, the most common disease among males in numerous countries, raises the difficulty of finding reliable screening tests. Most screening programs use free and total PSA testing. Serum human kallikrein-2 (hK2) may be a sign for predicting malignancy, so the optimal course of action, observation or biopsy, may be taken. August–October 2022 case-control study had 90 participants over 40 years; 60 prostate cancer patients and 30 healthy people of the same age and gender. Total, free prostatic specific antigen, human kallikreins-2, lipid profile, and blood glucose were examined. Results of the current study showed that there were higher mean serum concentrations of the total, free prostatic-specific antigen, human kallikreins-2, lipid (TC, TG, LDL, VLDL) profile, and blood glucose in patients than in healthy groups, while HDL was low in patients compared to control. Also, there were highly significant differences between the two groups with regard to the serum concentration of these variables. In addition, there was a positive correlation between human kallikreins-2 and free prostatic-specific antigen in patients with prostate cancer. Both free and total prostatic-specific antigens play a significant role in the diagnosis of prostate cancer, and human kallikreins-2 may be capable of enhancing early diagnosis by increasing specificity and reducing false-positive results from biopsies.

2022, 57 pages

Keywords: Prostate disease, Free PSA , Random blood sugar, Triglycerides

ÖZET

IRAK'TA BİR EĞİTİM HASTANESİNİ ZİYARET EDEN 40 YAŞ ÜSTÜ HASTALARDA PROSTATA ÖZGÜ ANTİJENLERİN (TOPLAM VE ÜCRETSİZ) DÜZEYİNDEKİ ARTIŞ PREVALANSI OLGUSU

Ibrahim Nayyef Ibrahim IBRAHIM
Kimya Yüksek Lisans
Tez Danışmanı: Doç. Dr. Şevki ADEM
Kasım 2022

Pek çok ülkede erkekler arasında en sık görülen hastalık olan prostat kanseri, güvenilir tarama testleri bulmayı zorlaştırıyor. Çoğu tarama programı ücretsiz ve toplam PSA testi kullanır. Serum insan kallikrein-2 (hK2), maligniteyi öngörmek için bir işaret olabilir, bu nedenle optimal eylem, gözlem veya biyopsi yolu alınabilir. Ağustos-Ekim 2022 vaka kontrol çalışmasında 40 yıl boyunca 90 katılımcı vardı; 60 prostat kanseri hastası ve aynı yaş ve cinsiyette 30 sağlıklı insan. Toplam, serbest prostat spesifik antijen, insan kallikreins-2, lipid profili ve kan şekeri incelendi. Mevcut çalışmanın sonuçları, hastalarda toplam, serbest prostata özgü antijen, insan kallikreins-2, lipid (TC, TG, LDL, VLDL) profili ve kan glukozunun ortalama serum konsantrasyonlarının sağlıklı gruplara göre daha yüksek olduğunu göstermiştir. kontrole kıyasla hastalarda HDL düşüktü. Ayrıca, bu değişkenlerin serum konsantrasyonu açısından iki grup arasında oldukça önemli farklılıklar vardı. Ayrıca prostat kanserli hastalarda insan kallikreins-2 ile serbest prostata özgü antijen arasında pozitif bir korelasyon vardı. Hem serbest hem de total prostata özgü antijenler, prostat kanseri tanısında önemli bir rol oynar ve insan kallikreins-2, özgüllüğü artırarak ve biyopsilerden alınan yanlış pozitif sonuçları azaltarak erken tanıyı güçlendirebilir.

2022, 57 sayfa

Anahtar Kelimeler: Prostat hastalığı, Serbest PSA, Rastgele kan şekeri, Trigliseritler

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Ibrahim Nayyef Ibrahim IBRAHIM

Çankırı-2022

CONTENTS

LIST OF SYMBOLS

-	Minus
/	Per
+	Plus
µL	Microgram
mg	Milligram
mL	Milliliter
ng	Nanogram

LIST OF ABBREVIATIONS

ACPT	Acid phosphate testicular gene
AR	Androgen receptor
ARE	Androgen receptors elements
ARR	Androgen responsive region
BMI	Body mass index
BOB	Bladder outlet blockage
Bp	Base pair
BPH	Benign prostate hyperplasia
DNA	Deoxyribonucleic acid
DRE	Digital rectal examination
FDA	Food and Drug administration
fPSA	free prostatic-specific antigen
HDL	High-density lipoprotein
Hk-2	Human Kallikriens-2
KLK	Kallikrien
LDL	Low-density lipoprotein
LUTS	Lower urinary tract symptoms
PC	Prostate cancer
PDEF	Prostate-Derived Ets Factor
PSA	Prostatic-specific antigen
RP	Radical prostatectomy
Sg-I	Seminoglein-I
TC	Total cholesterol
TG	Triglycerides
tPSA	total prostatic-specific antigen
TRUS	Trans-rectal ultrasonography
VLDL	Very low-density lipoprotein

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1. INTRODUCTION

The prostate is really an “exocrine gland” that is a constituent of the male reproductive organs. It is composed of muscle tissue in addition to glandular tissue. It may be found just ahead of the rectum as well as slightly underneath the bladder. It is wrapped around a portion of the urethra and approximates the size of a walnut. The fluid that is included in the semen is produced by the prostate gland (Byrne 2016). The commonness of “prostate cancer” is significantly higher in less developed nations, making it the fourth most popular type of cancer in generally and the most popular form of malignancy into men that is not related to the skin. It is also the second major reason of death from the cancer among men through the United States (Simfrosh and Noralizadeh 2007). The microscopic identification of prostate adenocarcinoma is largely based on particular characteristics of glandular development and pattern. The glandular genesis of prostate cancer accounts for about a 98percent of all instances of the disease. With the use of this categorization, urologists are able to stratify prostate cancer on a histopathological basis, which supplies them with crucial prognostic information. The Gleason score is the grading technique that is most widely acknowledged and utilized. The preponderance of prostate tumors has an average of a minimum of two geographically separate foci with different histological patterns and, as a result, different Gleason scores (Greenberg 2003). This is due to the fact that prostate cancers are multifocal in origin. Usually will patients have symptoms in the early stages of the prostate cancer since the vast preponderance of prostate cancers originate on the gland's periphery, away from of the urethra that drains the prostate. The development of symptoms almost often indicates either local expansion or potentially metastatic illness. The development of obstructive nullifying symptoms, which may include hesitation, reduction of the urine stream, and inconsistent flow, frequently follows the progression of cancer that has spread to the urethra as well as the neck of bladder. Intense annulling indications such as urgency and recurrence are also possible, however, they are harder to link to cancer due to they are also linked to “benign prostatic hyperplasia (BPH)”. Patients may experience hematospermia perhaps with reduced ejaculatory quantity because of ejaculatory duct occlusion as the tumor progresses, which are sexual symptoms. When

there is a regional intrusion on the neurovascular bundles, sexual dysfunction could also be noted (Clarke *et al.* 2009). The "prostate-specific antigen", often known as PSA, is a biomarker that may be used in the diagnosis of both benign and also malignant disorders that affect the prostate. It is well knowledge that determining the quantity of this protein is an important step in the diagnostic process as well as screening process for individuals who have prostatic cancer (Hori *et al.* 2013). PSA is a serine protease that belongs to the family of proteins recognised as tissue kallikrein. that will be generated by epithelial cells that are located in the prostate. Its primary purpose is to hydrolyze the proteins with large molecular weight that are secreted via the seminal vesicles, which in turn makes it possible for the spermatozoa to be released from the coagulum (Mawhinney and Mariotti 2013). In most cases, the concentration of PSA with in serum is rather little. When the natural structural design of the prostate gland is altered in any way, for example by prostatic illness, inflammation, as well as trauma, this makes it possible for higher quantities of PSA to reach into general circulation. An elevated PSA concentration in the blood has emerged as a significant diagnostic indicator for a wide variety of prostate disorders, particularly "benign prostatic hyperplasia", inflammation, in addition to prostate cancer (Shahab *et al.* 2013). Initially, it was believed that this protein was just generated by the prostate, but research findings have shown that it is expressed via a diversity of tissues in addition to the prostate, and it has been suggested that this protein may be a possible biomarker for cancer diseases other than the prostate (Pérez-Ibave *et al.* 2018). Previous research has investigated the link among PSA and a variety of the symptoms associated with metabolic syndrome, including increase levels of blood sugar, elevated concentrations of lipidis in blood, as well as obesity (Liu *et al.* 2011, Yang *et al.* 2012). Fatty liver disease, which is common in obese persons, may have an effect on the metabolic activities of PSA because the liver is the primary organ responsible for the breakdown and elimination of PSA (Yang *et al.* 2010). However, because of their increased plasma volume plus diluted blood, obese men may well have reduced PSA levels. It is also believed that testosterone metabolism, which is influenced by lipid levels, might alter serum PSA levels (Waters *et al.* 2009). According to previous research, the PSA levels of obese individuals with elevated body mass indices (BMIs) were lower than those of normal people (Hekal and Ibrahiem 2010, Wright *et al.* 2011).

1.1 Aims of the Study

The objectives of this research was to estimate the profile of human kallikrein protein, prostate-specific antigen among patients who were diagnosed with prostatic cancer. This profile comprises total, and free forms of the protein. Investigate the impact of the body mass index onto serum concentrations of the prostate specific antigens in addition to analyzing their associations with other metabolic diseases such as blood sugar and lipid profile.

2. LITERATURE REVIEW

2.1 Anatomy of the Male Reproductive System

2.1.1 Testes

The testes include a large number of convoluted seminiferous tubules, which are responsible for the manufacture of sperm. The wall of these tubules is made up of growing germ cells known as Sertoli cells. Interstitial cells, also known as Leydig cells, are the cells that produce testosterone. These cells may be found in the microscopic areas of connective tissue that are found between the tubules (Silverthorn 2015).

2.1.2 Epididymis

The epididymis is composed of one long, stretched tubule that is situated on the dorsolateral side of the testicle. It is functionally separated into three major components, which are as follows: The primary purpose of the caput (also known as the head) is to increase the number of viable spermatozoa by up to a factor of one hundred via the resorption of testicular fluid as well as spermatozoa of lower quality. A significant component of this part is the post-testicular maturation of the sperm corpus, often known as the sperm body. The cauda, also known as the tail, is primarily responsible for sperm storage, since about 70 percent of all spermatozoa are kept in this region. In addition, spermatozoa that are of low quality are resorbed in this region (Esteves and Agarwal 2016).

2.1.3 Seminal vesicle

The seminal vesicle is composed of a pair of convoluted tubes that measure between 3 and 4 millimeters in diameter and 5 to 6 centimeters in length. It is situated on the dorsal surface of the bladder where it may be found. The aperture of the ductus deferens may be found right below the ampulla of the ductus. Fructose as well as

prostaglandins are the only two substances that are ever expelled from this multiglandular organ. Seminal vesicles are responsible for 70% of the total amount of ejaculate and are responsible for delivering the last percentage of spermatozoa (Obukohwo *et al.* 2021).

2.1.4 Cowper's gland

The gland seems to be a pair of complex tubular glands that are about the size of a pea, are normally mucous, and are positioned just beneath the prostate (Silverthorn 2015).

2.1.5 Glands of littre

periurethral glands that are considered to be extremely tiny in size, it is believed that the "Cowper's gland" and the gland of Littre work to lubricate the urethra (Chughtai *et al.* 2005). The reproductive system of the man as seen in (Figure 2.1).

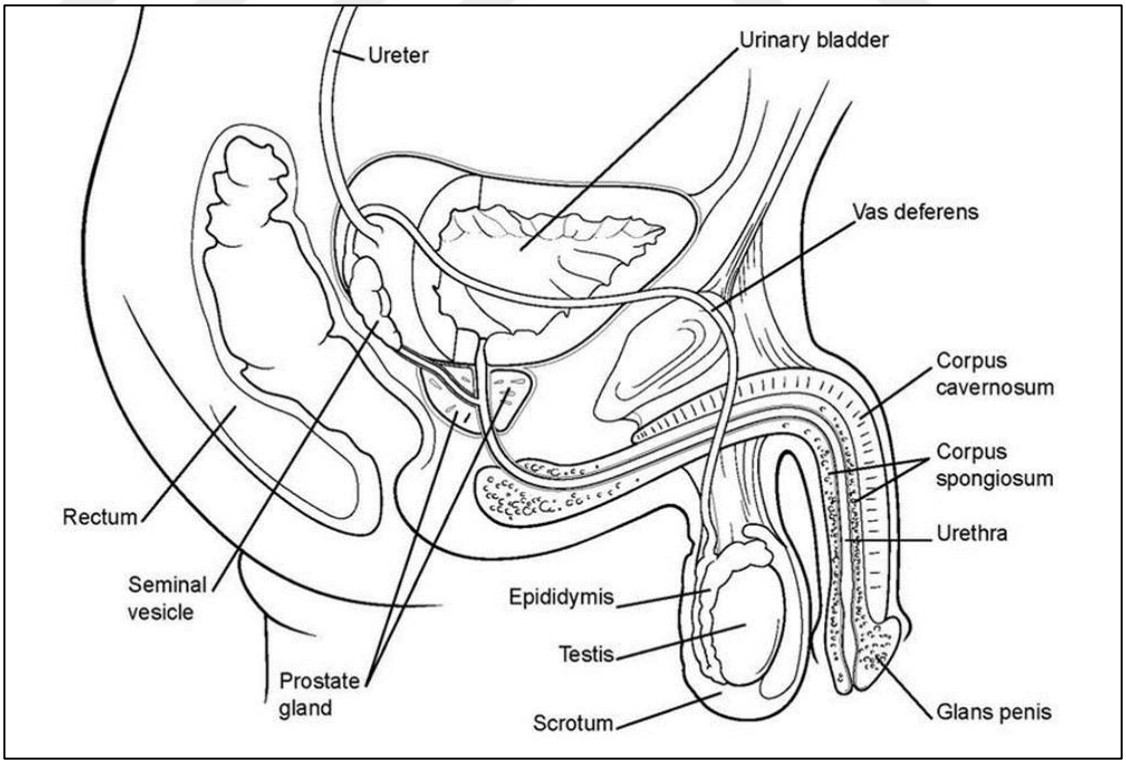

Figure 2.1 Parts of male reproductive system (Deepachandi 2012)

2.1.6 Prostate

Within the reproductive system of male, the prostate is the auxiliary gland that is the greatest in size. It is often accepted that a healthy human prostate is somewhat bigger than a walnut. Around eleven grams is the typical range for the weight of a normal prostate, which may be anywhere from Seven to Sixteen grams (Ismail 2015). It is a complex "tubule-alveolar exocrine gland" that is situated undermeath the bladder and ahead of rectum, and it is perforated via the urethra as well as ejaculatory ducts. The urethra inaddition to the ejaculatory ducts pass through it. It is accountable for the production of white fluid with a slightly alkaline that has a pH of 7.29 and accounts for 17% of the seminal plasma. Sperm cells are preserved, transported, and nourished by this fluid, which is abundant with "lipids, polyamines, proteolytic enzymes, acid phosphatase, fibrinolysis, as well as citric acids". In addition, this fluid shields and transports the sperm (Ismail 2015).

2.2 Prostatic cancer (PC)

Cancer is a condition that affects cells, which are the fundamental components of all tissues in the body. The order for making new cells then governing how existing cells perform are encoded and stored inside of cells. Genes are what we call the instructions themselves. Prostatic cancer (PC) develops when normally functioning cells start to proliferate more quickly or die off more slowly. Some cases of PC are caused by alterations in the genes, which are referred to as mutations. There are three basic ways in which cancer cells do not act normally like other cells. To begin, the modifications in genes lead normal prostate cells to develop at a faster rate and to survive for a longer period of time. Normal cells first develop, and then, when necessary, they divide to generate new cells. They might also perish due to old age or harm. On the other hand, cancer cells constantly produce new cells, even when they are not required, and they do not die off easily when they get old or damaged. Over the course of time, cancer cells aggregate into a mass that is referred to as the original tumor (Gurel *et al.* 2014). The second approach in which the cancer cells are distinct from the normal cells is in the manner in which they may spread into and infect the tissues of other organs. If the

initial tumor is not treated, it has the potential to get enormous and consume the majority of the prostate. Additionally, it is capable of growing outside of the prostatic capsule and invading neighboring tissues. Extracapsular extension is the term for this kind of growth. Third, in contrast to regular cells, cancer cells have the ability to go outside of the prostate. This is known as metastasis. After this, PC might metastasis to the additional areas throughout the body and begin to build tumors there. PC has the potential to spread via the blood stream as well as lymph vessels that are located inside prostate. The majority of men who are diagnosed with the prostate cancer will not pass away from the illness. On the other hand, prostate cancer is cosidered the second reason of the death of cancer among males. The majority of PCs have a modest growth rate, but there are a few that are aggressive and expand quite rapidly. The rapid expansion of certain personal computers is a mystery that experts are attempting to solve (Carroll *et al.* 2015).

2.2.1 Epidemiology of prostatic cancer

Cancer of the prostate is still one of the popular prevalent kinds of cancer to strike men through our day and age. It is the third most popular frequent cancer into the world, and among males in Western nations, it is considered the second reason of death resulting from cancer (Parkin *et al.* 2001). The rates at which prostate tumors are detected varies greatly from one region of the globe to another, with Asia having one of the lowest rates in comparison to Europe and notably the United States (Khudur 2012). In several Asian and European nations, both theoccurence of the prostate cancer and the death rate due to this disease are on the rise (Chornokur *et al.* 2011). Throughout the United Kingdom, a total of 34,302 men were identified as having prostate cancer in 2005, and then in 2006, 10,038 men passed away as a direct result of the condition (Burford *et al.* 2009). Alterations in lifestyle have contributed to an increase in the prevalence of the illness among the Arab population. Between the years 1991 and 2006, prostate cancer was the most popular kind of the cancer found into Qatari men aged 65 as well as older (Bener *et al.* 2008). The annual rate of prostate cancer diagnoses reached 12.3/100,000 males in Kuwait in 2004, marking a significant increase from previous years (Kehinde *et al.* 2006). Throughout Tunisia, “prostate cancer” was the fourth most prevalent form of the

disease to be detected in the year 2003 (Shan *et al.* 2013). During 1998, the prevalence of the prostate cancer was recorded as 21.5 cases per 100,000 males through Lebanon (Shamseddine *et al.* 2004). Although Iraq, prostate cancer accounts for 3.3% of recently diagnosed instances of cancer among men and is the top reason of cancer among males (Espey *et al.* 2007).

2.2.2 Benign prostatic hyperplasia (BPH)

According to a research conducted into United States, “benign prostatic hyperplasia” (also known as BPH) is one of the ten disorders that are the most common and expensive to treat in males above the age of 50 years. “Lower urinary tract symptoms (LUTS)” are most often brought on by benign prostatic hyperplasia (BPH), which may also bring on bladder outlet blockage (BOB) (Parsons, 2010). BPH is considered a benign (non- malignant) expansion in the prostate diameter. BPH includes hyperplasia of the prostatic epithelial also stromal cells, which causes the development of big, rather separate nodules within the transition zone of prostate. BPH is the common cause of enlarged prostates among men above age of 60 years. Whenever they reach a certain size, the nodules might press on the urethra, which causes an increase in the amount of resistance to the flow of urine out of the bladder (Sodani 2018). The urethral lumen is not any less patent, merely compressed, despite the fact that this condition is frequently referred to as "obstruction." When there is a blockage in the urinary tract, the bladder has to work harder to empty itself, which may eventually result in increasing hypertrophy, instability, and even atony (weakness) of the bladder muscle. The condition known as “benign prostatic hyperplasia (BPH)” is described by hyperplasia, which is a rise in the cells number, as opposed to the hypertrophy, which is a expansion in the cells size, nonetheless, the two words are sometimes emploed alternatively, even between the urologists (Wilt *et al.* 2012). Even while the levels of prostate-specific antigen in these individuals may be higher as a result of increased organ size as well as inflammation brought on by urinary tract infections, BPH doesn't really cause cancer nor does it raise the risk of cancer. It is considered that the development of adenomatous prostatic growth begins somewhere around the age of 30. It is expected that 50 percent of men will have histologic sign of BPH in the age of 50 years, and 75 percent will have

it in the age of 80 years. Forty to fifty percent of these men will have symptoms. When symptoms of BPH become noticeable in a clinical setting. Symptoms include abdominal pain, a person feels of having a full bladder at any time, increased urination, acute urinary retention, pain throughout urination, difficulty urinary hesitancy, a sluggish urine stream, beginning as well as stopping urinary and nocturia. BPH is a condition that may worsen with time, particularly if it is not managed. If you don't completely empty your bladder, you'll end up with urinary stasis, also known as residual pee, which puts you at an elevated risk of developing an infection in your urinary system (Skinder *et al.* 2016). Benign prostate hyperplasia (BPH) and normal anatomy is shown in (Figure 2.2).

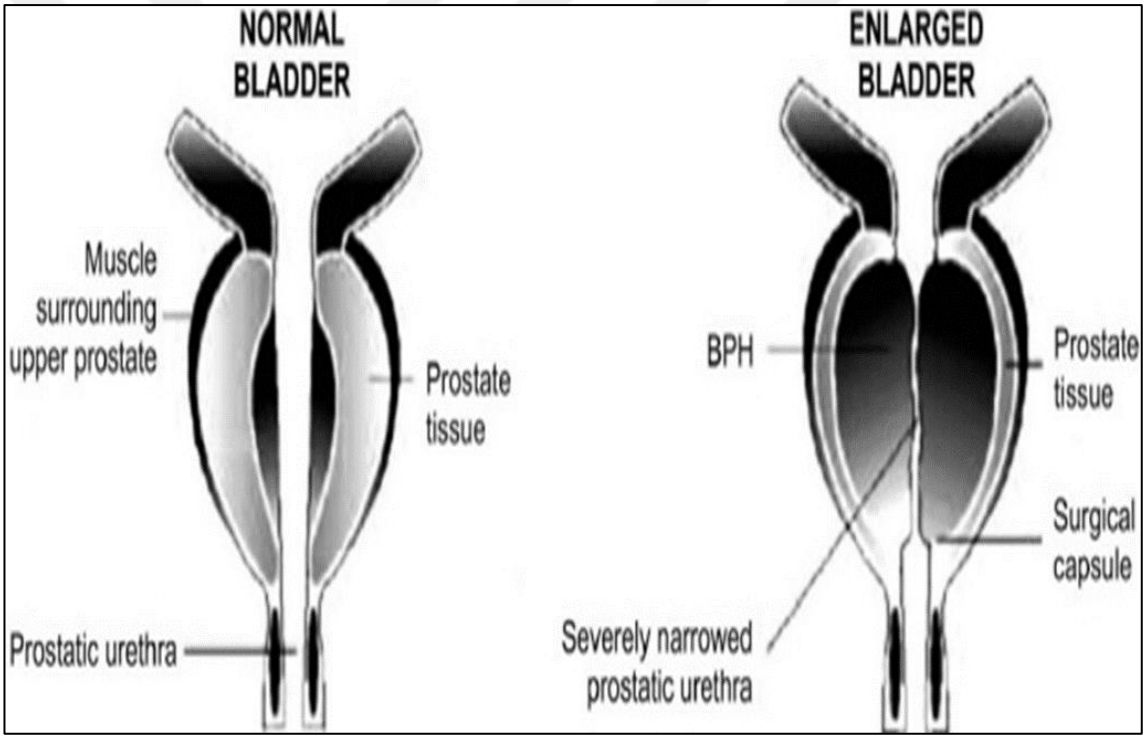

Figure 2.2 Demonstrated normal and benign prostate hyperplasia anatomy in men (Dhingra and Bhagwat 2011)

2.2.3 Malignant cancer of prostate

There are a several other kinds of cells that may be discovered in the prostate, but nearly majority PCs originate from gland cells, which are cells that are responsible for

producing the prostate fluid that is combined with the sperm. Adenocarcinoma is the name given in medical parlance to cancer that originates in gland cells. Different forms of cancer, including as the |sarcomas, also small cell carcinomas, as well as transitional cell carcinomas", may also begin within prostate gland where they can expanse to other paositions of the body. If you do have a cancer of the prostate, however, it is almost always an adenocarcinoma. This is because the other forms of PCs are so uncommon. There are PC that can multiply and spread rapidly, but the most majority multiply quite slowly (Terry and Beltran 2014).

2.2.4 Cancer of the prostate risk factors

Anything that increases one's likelihood of developing an illness, such as cancer, is referred to as a risk factor. There are several types of cancer, each with its own unique set of risk factors Tobacco use, age, nutrition, race/ethnicity, history of the family, geographic location, obesity, alterations within gene, cigarettes smoking, occupational risk of exposures,and sexually transmitted diseases, prostate inflammation, as well as the vasectomy are the risk factors (Kreitler 2019).

2.2.5 Grading of prostate cancer

The term "Prostate Cancer Grade" indicates the degree to which cancer cells identical to the normal cells. The severity of the malignancy might provide insight to the treating physician on the rate at which the disease will progress. The "Gleason system" is the most widely used grading system also provides a description of the cell patterns that may be viewed under a microscope (Droz, 2013).

2.2.6 The staging of prostatic cancer

The term "staging" refers to a method of characterizing cancer, including aspects such as the size of the tumor as well as the locations to which it has spread. When it comes to determining a patient's prognosis, staging is the most essential tool that clinicians have

at their disposal. The TNM method is used to stage cancers by describing factors such as the size of the tumor and whether or not the malignancy has metasted to adjacent lymph nodes. And if cancer has gone to other organs like the liver and\or lungs, and whether the tumor has expand to other organs, and if the cancer has metastasized to distant . In yet different staging method, letters are assigned (A, B, in addition C and D). The stage of cancer determines the sort of therapy that will be administered to a patient (Shroff *et al.* 2018).

2.2.7 The anatomical stage and development of malignant prostate cancer

The cancer known as stage 1 of malignant prostate cancer can only be identified in the prostate, and its growth is often quite sluggish at this stage. The prostate cancer in stage 2 has not yet metastasized beyond the gland, but it has spread to several areas inside the prostate and may progress more rapidly than cancer in earlier stages. The cancer has progressed to stage three and has gone outside the surface of prostate to the neighboring tissues or may be to the seminal vesicles, which are glands that contribute to the production of sperm. Lastly, the cancer has gone to other positiions of the body, like bladder, rectum, bone, liver, lungs, or lymph nodes. Stage foure cancer has reached this point when it has spread across the body (Pezaro *et al.* 2014). (Figure 2.3) showed the anatomical of prostatic stages cancer.

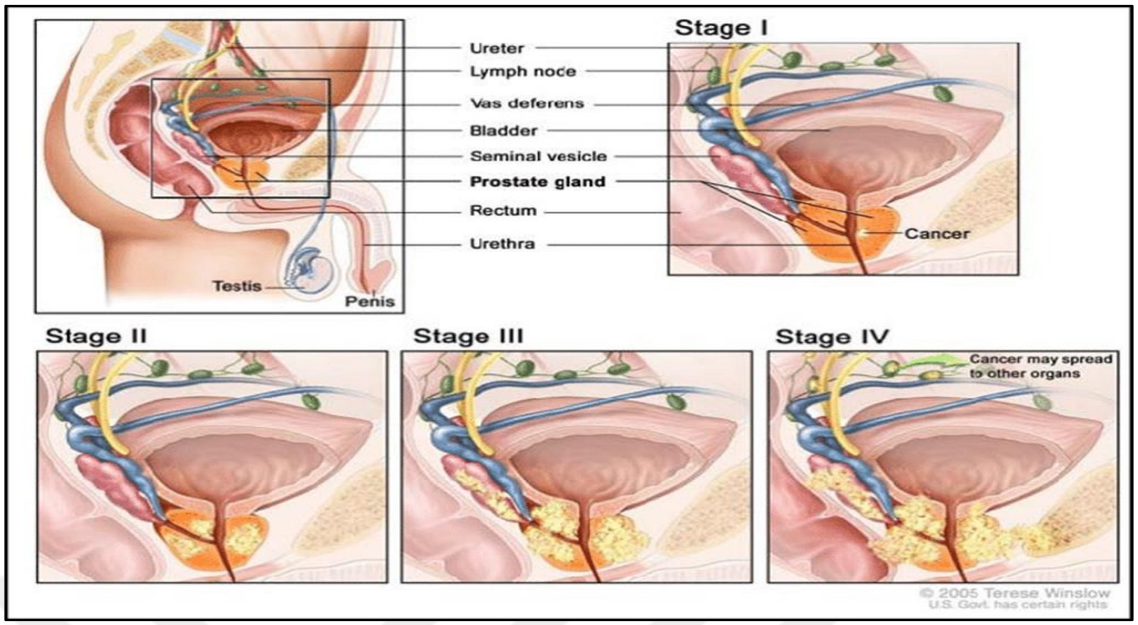

Figure 2.3 Anatomical of prostatic cancer stages (Pezaro *et al.* 2014)

2.2.8 Clinical features of prostatic cancer

In its early stages, prostate cancer (PC) almost never produces any symptoms. However, more advanced PC may sometimes induce symptoms, including the following: difficulties urinating, such as a slow as well as vulnerable urinary flow or the requirement to urinate more frequently, particularly during the night, blood with in urine, difficulty obtaining an erection (impotence), pain within thighs, back, chest, or even other areas from cancer spreading to bones, lack of strength or loss of sensation in the legs or feet, or perhaps even loss of the bladder and bowel regulate from the cancer pushing on the spinal cord (Kwast and Roobol 2013). Many of these symptoms may also be brought on by a variety of other diseases. For instance, “benign prostatic hyperplasia (BPH)” is a far more common reason of the urinary dysfunction than malignancy (Kristal *et al.* 2014).

2.2.9 Identification of prostate cancer

Through the estimaing the concentration of “prostate-specific antigen (PSA)” in a man's blood, doctors are typically able to diagnose the “prostate cancer (PC)” during its early

stages. “Digital rectal examination(DRE)” is another method for detecting PC at an early stage. If the outcomes of any of these exame come back abnormal, then you will need to undergo further testing to determine whether or not you have cancer. If prostate cancer is detected by investigating with either PSA or DRE, it will most likely be at an earlier stage when it is easier to treat than if screening weren't done at all (Catalona *et al.* 1994).

2.3 Prostatic Specific Antigen (PSA)

The “prostate-specific antigen (PSA)”, is a biomarker that is used in the diagnosis of benign as well as the malignant illnesses of the prostate gland (Rao *et al.* 2008). It is well acknowledged that the measurement of this protein serum level utilized for the identification and surveillance of the prostatic cancer patients. Additionally, this protein constituted the first tumor biomarker that was authorized by the “Food and Drug Administration (FDA)” (Diamandis 2000). PSA is considered a serine protease that belongs to the family of proteins known as tissue kallikrein. epithelial prostatic cells are responsible for the production of this (Yousef and Diamandis 200"1). Its primary purpose is to hydrolyze the proteins with a large molecular weight that are secreted by the seminal vesicles, which makes it possible for the spermatozoa to be released from the coagulum. Initially, it was believed that the prostate was the sole organ capable of producing this protein (Lamirande 2007). Nevertheless, there are a number of studies that demonstrate that this protein is produced by numerous tissues that are outside the prostate, and it has been suggested that it may be a viable biomarker to the cancer pathology other than those of prostate gland (Diamandis and Yu 1997). According to the findings of certain writers, the expression of this protein in females is strongly linked to a number of different cancers, one of which being breast cancer, as a result, this protein could serve as a potential biomarker (Mashkoor *et al.* 2013). However, some authors have shown that measurable amounts of PSA may be found in the blood of women who do not have breast illness or a benign form of breast disease, hence, more study is required (Melegos and Diamandis 1998).

2.4 Kallikrein Locus Organization, Gene Structure and Regulation of PSA

PSA belongs to the family of proteins known as tissue kallikreins. The “kallikreins” are a class of serine proteases that may be discovered in a variety of tissues in addition to biological fluids (Yousef and Diamandis 2001). There are 15 genes in the human kallikrein locus (KLK genes). grouped in tandem arrays along a three-hundred kb area nearby the (19q13.3-q13.4) region of chromosome 19. The gene for testicular acid phosphatase (ACPT) binds to this locus in a centromeric orientation, while a gene linked with cancer does the same in a telemetric orientation, as well as Siglec-9, which is a member of the group of sialic acidbinding Ig-like lectins. All of the genes KLK4-KLK14, as well as the pseudogene KLK1, are positioned telomeric to the KLK2 gene. With the exclusion of the KLK3 as well as KLK2, the pathway of transcription for each of the KLK genes is from the telomere towards the centromere. The KLK3 gene, also known as PSA, is 5846 base pairs long. It is made up of 5 exons plus 4 intervening introns, and it has a phase pattern for its introns that is always the same (I, II, I, 0) (Borgono *et al.* 2004). A first coding exon contains a short 5'-untranslated regions, and 2nd exon contains the amino acid (histidine) of the catalytic trial in the direction of the extreme of exon, while third exon contains the (aspartic acid) of the catalytic triad round the central portion of exon, and the 5th exon contains the serine of the catalytic triad at the start of exon. All of these exons are part of the catalytic triad. There is a 3'-untranslated region that may be found after the stop codon (Yousef and Diamandis, 2001). As illustrate in (Figure 2.4).

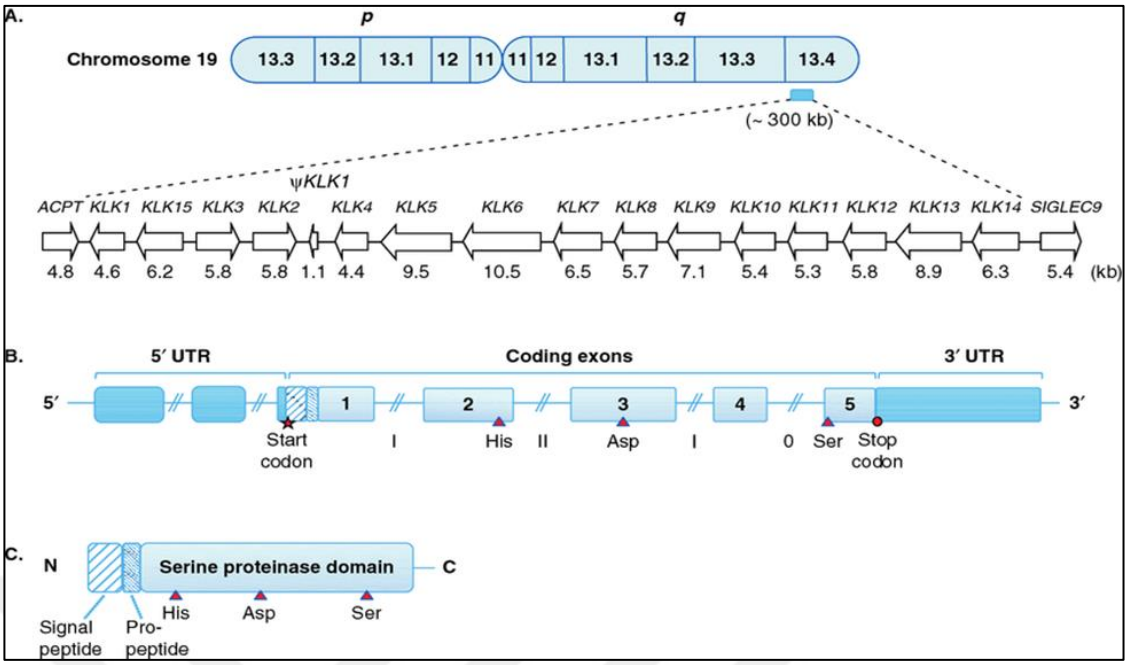

Figure 2.4 Human tissue kallikrein family gene locus, organization pattern, and protein properties (Chang *et al.* 2007)

Androgen receptors have a beneficial influence on the expression of the PSA gene via regulating its transcription. Androgens are responsible for their effects because they interact with the "androgen receptor (AR)", which belongs family of the steroid hormone receptors. Upon the binding of ligand, the AR becomes an important transcription factor. changes its conformation when it moves from the cytoplasm to the nucleus of the cell. where it modulates the transcriptional activity of target genes, particularly PSA, by interacting with certain DNA sequences and directing how they are read (Tyagi *et al.* 2000). It has been discovered that the sequences of DNA in which the steroid receptors engage are flawed palindromic sequences that are expand from one another via a spacer consisting of three base pairs. The response element for AR, as determined by the consensus sequence (called ARE) (Cleutjens *et al.* 1996). The length promoter of the PSA is 6 kilobytes, and it has a TATA box on -22 base pairs, upstream on -156 until -170, and there is a powerful element of AR. Additionally, AR is able to feebly bind at a different position that is distinct from the robust consensus ARE. The coordinates -366 until -400 include a sequence that has been dubbed the androgen -responsive region (ARR), and it can be found here (Cinar *et al.* 2004). In study of Schuur and colleagues, explain how they found and characterized an androgen-

responsive enhancer that was placed around 3,700 base pairs (bp) upstream from the beginning of the PSA gene's transcription process. The phrase "PSA distal enhancer" refers to this segment that is around 440 base pairs long. includes one extra ARE that has a strong consensus and five other AREs that do not have a strong agreement (IV, V, VI, IIIA, and IIIB) (Huang *et al.* 1999). Androgen is necessary for the differentiation and proliferation of normal prostate epithelia in addition to the early development of the prostate cancer cells. This need for androgen results in the activation gene of the PSA. The reduction in level expression of PSA, on the other hand, is suggestive of the progression of "androgen-sensitive prostate cancer (PCa)" into androgen-resistant prostate cancer (Crespo *et al.* 2015). The fact that some form of prostate cancer tumors are resistant to androgenic therapies is evidence that are found an additional mechanisms that control to expression of PSA independently on the androgens. One of these mechanisms is "Prostate-Derived Ets Factor (PDEF)" transcription factor, which operates in circumstance of an androgen-independent (Oettgen *et al.* 2000). Various transcription factors, such as NF-B, have been recognized as doing an androgen-independent role through process of the PSA control (Chen and Sawyers, 2002).

2.5 Function and Clinical Application of Prostatic Specific Antigen

The primary function of the PSA is to facilitate dissolution of seminal clots. Following ejaculation in humans, the sperm will begin to coagulate on its own. It is a concoction made up of spermatozoa as well as the fluids produced by a variety of male accessory sex glands (Robert and Gagnon 1999). This coagulum is generated mostly via proteins that originate from seminal vesicles. These proteins are "semenogelin I (Sg-I) as well as semenogelin II (Sg-II)". Fibronectin also contributes to the formation of this coagulum to a lesser degree. Twenty to forty percent of the seminal plasma proteins between 10 and 20 mg/mL) are composed of Sg-I and Sg-II. Following ejaculation, male spermatozoa are unable to move because they are stuck in the coagulum of the semen. The first stages of forward movement begin with the liquefaction of the sperm. During minutes following ejaculation, the semen coagulum will spontaneously liquefy, and up to this point, it has been determined that the "prostate-specific antigen (PSA)" is the enzyme that particularly manages Sg-I as well as Sg-II (Lamirande 2007). The

discovery by (Stamey *et al.* 1987) that there was a relation between PSA and advancement cancer of prostate marked the beginning of the utilize of PSA as a diagnostic biomarker to prostate cancer (Sokoll and Chan 1997). PSA is the oncological biomarker that is employed the most often in modern medicine, and it is also utilized as a screening approach for the identification of prostate cancer (Duskova and Vesely 2015). There is a correlation between the prostate size and the quantity of the glandular epithelium, which is also connected to the concentration of PSA. Therefore, if prostate cancer causes an rise in the size of prostate, there should also be an increase in the normal PSA concentration (Adhyam and Gupta 2012). Nevertheless, there are other characteristics, such as race, that can contribute to a rise in normal PSA levels. the body mass index, sometimes known as the BMI (weight tends to have a negative effect on PSA values). PSA levels may be lowered by using medications such as NSAIDs, statins, as well as thiazide. It has been observed that grows in size of the prostate related with advancing of age (Chang *et al.* 2010). Additional factors, including as a "digital rectal examination (DRE)", ejaculation, microbial prostatitis, a prostate biopsy, or acute urine retention, might also contribute to an increased PSA level (Tchetgen and Oesterling 1997). The grouping of PSA testing plus "digital rectal examination" results in an enhanced ability to identify prostate cancer and a shorter period before diagnosis. A helpful clinical method that boosts the predictive value of cancer diagnosis is the ratio among free\ total-PSA. The lower the percentage of "free prostate specific antigen (fPSA)", the greater the risk of developing prostate cancer. Moreover, there is a positive correlation between elevated concentration of (Fpsa) and benign prostatic tissue (Polascik *et al.* 1999). In individuals whose total PSA concentrations range from (4-10 ng/Ml) and who have a obviously benign gland, a cutoff of 25% fPSA in proportion of (fPSA/ tPSA) has been applied to determine whether or not the patient has prostate cancer. This not only enhances the accuracy of cancer detection but also raises the specificity of the test. To evaluate whether or not a patient with a typical "digital rectal examination" as well as a total-PSA concentration between (4 -10 ng/Ml), would advantage from a primary or rehash biopsy, had at least one former negative biopsy, the best suggestion for employing the proportion of the free-PSA is to detection whether or not patient has prostate cancer. It has been hypothesized that the complex- PSA (cPSA), has significant medical importance for the identification of prostate cancer.

PSA-ACT has been recognized as a tumor biomarker that increases the likelihood of detecting prostate cancer (Catalona *et al.* 1998). Various clinical indicators, such as PSA velocity or density, as well as the proportion of free-PSA, have been presented as ways to assist in making a more precise detection of prostate cancer (Djavan *et al.* 1999). Unfortunately, there is currently no general agreement about the use of any of these putative biomarkers for PSA, and none of them lower the number of needless biopsies or enhance medical procedures outcomes. Due to it catches clinically minor prostate illness also minimizes amount of needless for prostate biopsies, the measurement of total- PSA is remain regarded the gold standard (Adhyam and Gupta 2012). As a result, there is an increasing requirement to carry on with the proof of biomarkers that have been suggested up until now and to consider for additional blood biomarkers that permit diagnoses at primary stages as well as assist in predicting how patients will respond to treatment in order to conserve more lives (Alberts *et al.* 2015).

2.6 Relationship Between Obesity and Prostatic Cancer

The phrases "obesity," "diabetes mellitus," with "cardiovascular disease" are all part of the “metabolic syndrome” which is an assortment of risk factors which are intimately associated to progression of the obesity. The underlying pathophysiological processes are rather complicated. Some of these mechanisms include visceral obesity, atherogenic dyslipidemia, as well as endothelial dysfunction, although this list is not exhaustive (Huang 2009). When taken collectively, these risk factors have been related to an elevated risk of emerging a variety of the illnesses, particularly prostate cancer. Free fatty acids, also adipokines released by fat cells, activity of aromatase, resistance to insulin, as well as IGF-1 have all been hypothesized to have a role in the growing of obesity in addition to related diseases (Uzunlulu *et al.* 2016). Obesity, elevated blood lipid concentrations, and an elevated in risk of the prostate cancer which have been linked in a small number of researches (Bhindi *et al.* 2016). Although there was a substantial relatioship between prostate cancer with high-grade and elevated triglycerides (TGs) as well as low high-density lipoprotein (HDL) levels, this association did not hold true across all of the studies that were conducted (Chen *et al.* 2018). In addition to this, a low HDL was connected to unfavorable pathological results

following radical prostatectomy (RP) (Lebdai *et al.* 2018). Similarly, there is ample evidence that lifestyle factors perform a part in the progression of prostate cancer (Shiota *et al.* 2017).

3. MATERIALS AND METHODS

3.1 Materials

Kits for total, free-“prostatic specific antigen”, and human kallikreins-2 ELISA are included among the analytical reagents available. The total cholesterol, triglycerides, low-density lipoprotein, and a variety of substrates, in addition to any and all other materials, were all given by EAGLE, BIOSCIENCE, located in the United States of America, and Fujifilm, located in Thailand, respectively.

3.1.1 The subjects of studies

This case-control research was performed between the months of August and October 2022, and it included a total of ninety participants. All of the participants were at least forty years old, and they were split for two groups: First group comprised of sixty participants who were identified with the prostate cancer and were regular patients at Salah Al-Din Teaching Hospital, and the second group consisted of thirty healthy participants of the same age and gender. The research was conducted in conformity with the :”Helsinki Declaration on Human Rights and Medical Ethics”, which served as a statement of ethics for the study. Samples were taken after telling the patients and getting their explicit agreement to participate in this study as full-fledged volunteers.

3.1.2 Equipment and apparatus

Throughout the process of this thesis, a variety of apparatuses and pieces of equipment were employed, and Table 3.1 provides an explanation of some of these items.

Table 3.1 Employed apparatus and equipment for the research assignment

Equipment and apparatus	Identity and Ancestry
Centrifuge	Japan
ELISA apparatus	BioTek-US
Washer	BioTek-US
Immunofluorescence analyzer	Fujifilm-South Korea
Multichannel pipettes	Cleaver-USA
Pipettes	Cleaver-USA
Printer	Canon-USA
Refrigerator	China
Tips	China
Gel tube	China
Shaking-Water path	Taiwan

3.1.3 Sample collection from both research groups

After already being centrifuged for ten min then being preserved during room temperature for another 10 min, the specimens taken were deposited into an activator-coated gel tube. Every volunteer was requested to provide five milliliters of bloodstream. Following the separation of the serum, it was transferred to Eppendorf tubes then kept in the deep freezer at a temperature around minus 20 ℃ until the concentrations of total, free prostatic specific antigens and human kallikreins-2, total cholesterol, triglycerides, and high-density lipoprotein, in addition to blood glucose, could be assessed.

3.2 Methods

3.2.1 Measurement of total, free prostatic specific antigen profile and kallikrein-2

3.2.1.1 Principle of the procedure

A conventional "sandwich", as well as a two-step catch assay, is the basis for the enzyme immunoassay test that will be described in the subsequent paragraphs. The test takes utilize of two monoclonal-antibodies that are high-specific for the target. The

immobilization of monoclonal antibodies specific with total, free PSA in addition to kallikreins onto the microplate is followed by the conjugation of a second monoclonal antibody specific for a separate area of PSA with horse radish peroxidase (HRP). After allowing the PSA profile protein as well as kallikreins-2 from the specimen and standards to attach to the plate, washing it, and then incubating it with the HRP conjugate. Following the second round of washing, the enzyme substrate is then added. The application of the stopping reagent halts the enzymatic reaction and brings the process to an end. The microtiter plate reader is used to take the readings for the absorbance. The amount of PSA profile as well as Kallikreins-2 present in the specimen has a direct relationship with the degree of color that is produced by the enzyme reaction.

3.2.1.2 Procedure

1- In a separate set of wells that have been appropriately labeled, pipette 25 µL from each the calibrator, the control, and the experimental sample.
2- Each well should have one hundred microliters of the assay buffer pipetted into it.
3- Under room temperature, incubated for one hour using a plate shaker at a speed of roughly 200 revolutions per minute.
4- Wipe the plate gently on absorbent paper to make sure that it is dried after washing the wells three times with a total volume 300 µL from diluted wash buffer for each well.
5- Within every well, aliquot an amount equal to 100-microliters from conjugate working solution.
6- At room temperature, incubated for half an hour using a plate shaker at a speed of around 200 revolutions per minute.
7- Perform another round of cleaning on the wells.
8- At periodic times, pipette one hundred microliters of TMB substrate through every well.
9- 10–15 minutes were spent incubating the sample at room temperature while using a plate shaker.
10- Every of well should have 50 µL of the stopping solution pipetted into it.

3.2.2 Estimation of blood glucose

3.2.2.1 Principle

The enzyme glucose oxidase acts as a catalyst in the process of glucose being oxidized into hydrogen peroxide from the samples. In the presence of peroxidase, an interaction between hydrogen peroxide and dye precursors results in the production of a red dye. After incubating a slide at 37 degrees Celsius for a certain period of time, the optical density was measured at 505 nanometers.

3.2.3 Estimation of total cholesterol

3.2.3.1 Principle

The free molecule of cholesterol may be generated by the process of cholesterol esterase hydrolyzing the cholesterol ester. Free and endogenous cholesterol both contribute to the production of hydrogen peroxide when they interact with cholesterol oxidase Through order to generate a blue color dye, the leuco-dye must first be oxidized using hydrogen peroxide and then peroxidase. Furthermore, the optical density of the experiment was measured at 505 nm after the slide had been incubated for a certain period of time at 37 degrees Celsius.

3.2.4 Estimation of triglycerides

3.2.4.1 Principle of the measurement

LPL is responsible for the dehydrolysis of lipoprotein, which results in the production of glycerol, which then dissolves through the underlying layer. Throughout the reagent layer, the existence of GK caused glycerol to be transformed to glycerol-3-phosphate. Glycerol-3-phosphate-oxidase was therefore responsible for converting glycerol-3-phosphate into dihydroxyacetone-3phosphate. This process results in the production of

hydrogen peroxide, which is then used by peroxidase for oxidize diarylimidazole leuco dye, therefore producing the blue color dye After incubating the slide for a predetermined period of time at 37 degrees Celsius, the optical density was measured at 650 nanometers.

3.2.5 Estimation of high-density lipoprotein

3.2.5.1 Principle of the measurement

Insoluble complexes are formed when extremely low density lipoprotein and low density lipoprotein interact with dextran sulfate. When high density lipoprotein reacts with the surfactant, it separates into protein and lipid. Cholesterase converts cholesterol esters in lipids to cholesterols, while cholesterol oxidase oxidizes the produced cholesterol and endogenous cholesterols to make hydrogen peroxide. The coupling process between the 4-aminoantipyrine plus DAOS is initiated by peroxidase reacting with hydrogen peroxide, resulting in a blue color dye. The slide was incubated for a set extent of time through 37 °C, then optical density of test was detected at the 650 nm.

Each one of the aforementioned biochemical markers may be measured using an instrument called a full-automatic dry-chemistry analyzer, as well as the operation can be fully automated according to the instructions that were made for the equipment.

3.2.6 Estimation of low -density lipoprotein plus very low-density lipoprotein

The following Equation (3.1) and (3.2) were used throughout the course of the assessment:

$$VLDL\ \left(\frac{mg}{dL}\right) = \frac{TG}{5} \tag{3.1}$$

$$LDL\ \left(\frac{mg}{dL}\right) = \ (cholesterol - HDL - VLDL) \qquad (3.2)$$

3.2.7 Statistical analysis

When describing the findings of an investigation, statisticians often use to terms like the Midian, the Percentile 05, as well as the Percentile 95. The Mann-Whitney test is a statistical technique that may be used to compare groups whose dispersion is skewed. It was named after the two statisticians who developed it. If the P-value is to be regarded statistically meaningful, it must be less than 0.05, and this threshold must be met before the data can be declared conclusive. For the purpose of inspecting and validating each and every result, the statistical software SPSS 20.0 was utilized.

4. RESULTS

4.1 Characteristics Data of Patients and Healthy Groups

This study included ninety participants in the Salah al-Din Governorate -Iraq. They were catigorized for two groups. First group included sixty members who were identified suffering from prostate cancer, while second group included 30-healthy participants as a control healthy group. The age of the participants was over forty years, with an average age of 57.13±8.76 years for the healthy group and 56.11±8.68 years for the patient group. Where there was not founf significant difference between groups with regard to age, as demonstrated in the Table 4.1 and Figure 4.1.

Table 4.1 Age distribution

	Study groups	Mean	Std. Deviation	p value
Age (years)	Control	57.13	8.76	0.472
	Patients	56.11	8.68	

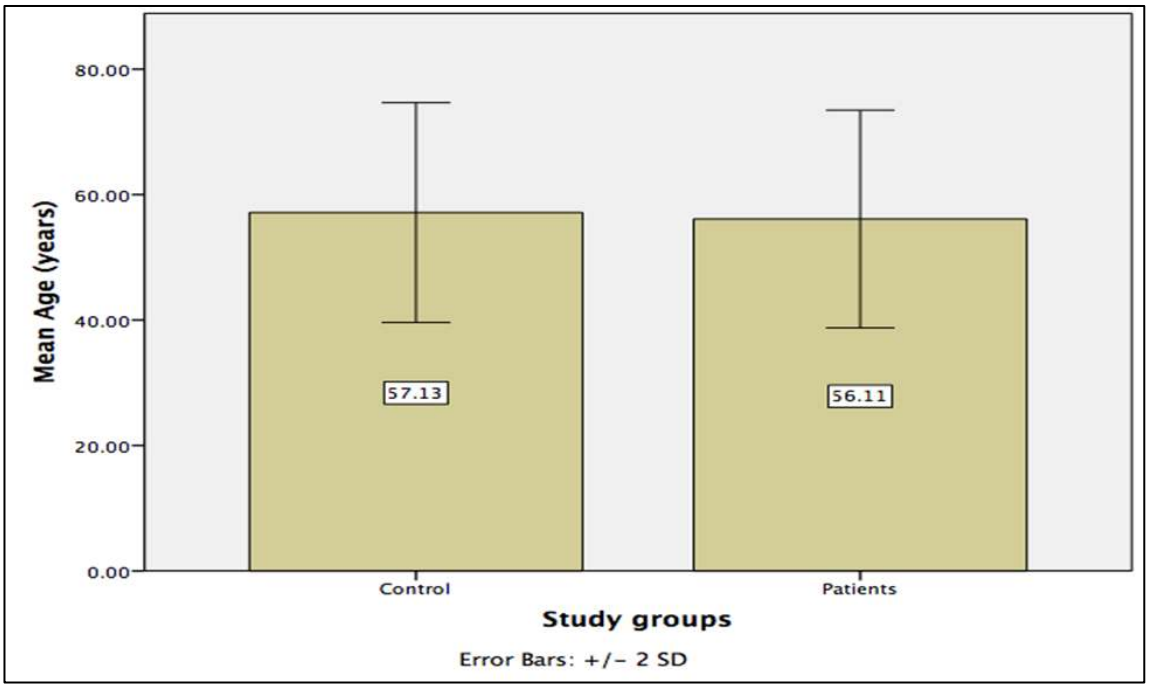

Figure 4.1 Age distribution

4.2 Prostatic Cancer Markers

4.2.1 Total prostatic-specific antigen (TPSA)

Table 4.2 and Figure 4.2 show that there was a highly difference between mean of serum concentration of total prostatic-specific antigen between the group of patients and the healthy group (1.08±0.13, 0.53±0.06 ng/ml), respectively. In addition, there was highly significant disparity between groups (p- less than 0.001**) during this present study in regard to serum concentration of TPSA.

Table 4.2 Serum concentration of total prostatic-specific antigen

	Study groups	Mean	Std. Deviation	p value
Total PSA (ng/ml)	Control	0.53	0.06	<0.001**
	Patients	1.08	0.13	

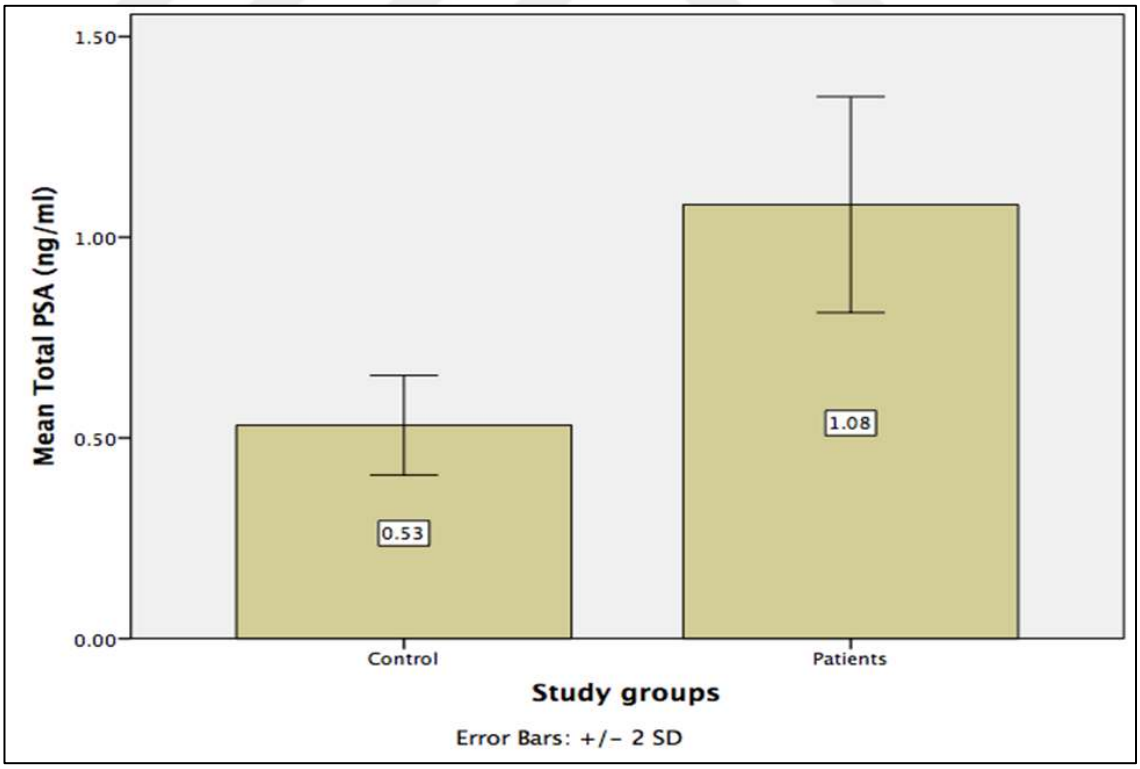

Figure 4.2 Serum concentration of total prostatic-specific antigen

4.2.2 Free- prostatic-specific antigen (Free PSA)

The mean serum concentration of the free prostatic-specific antigen between the illness group and the healthy group is markedly different (0.33±0.06, 0.163±0.03 ng/ml, respectively) as shown in Table 4.3 and Figure 4.3. Additionally, there was highly discernible variation in the serum levels of free PSA between groups in this investigation (p-less than 0.001**).

Table 4.3 Serum concentration of free prostatic-specific antigen

	Study groups	Mean	Std.	p value
Free PSA (ng/ml)	Control	0.16	0.03	<0.001**
	Patients	0.33	0.06	

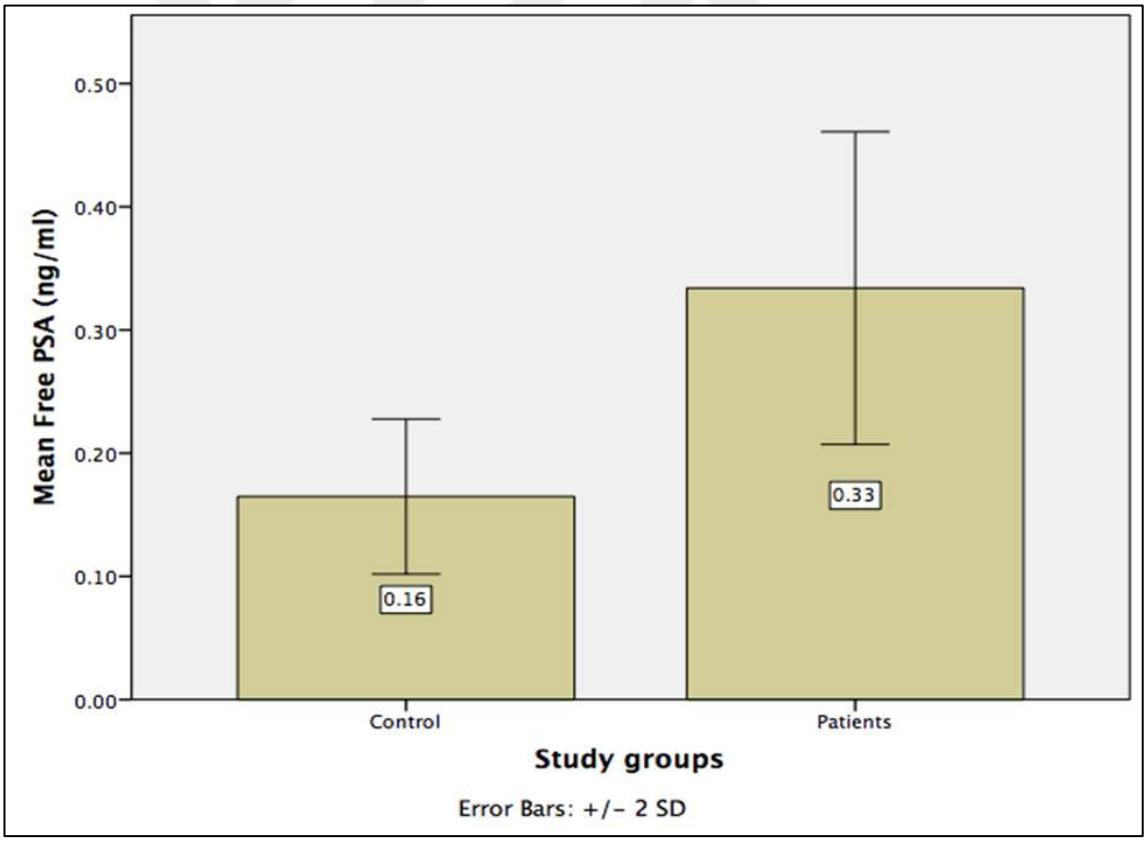

Figure 4.3 Serum concentration of free prostatic-specific antigen

4.2.3 Kaliilkreins-2

Table 4.4 and Figure 4.4 show that there is a mild difference between the mean of serum concentration of the Kaliilkreins-2 between the group of patients and the healthy group (0.04±0.01, 0.03±0.00 ng/ml), respectively. In addition, there was significant variation between groups (p-less than 0.001**) during present study in regard to serum concentration of Kaliilkreins-2.

Table 4.4 Serum concentration of Kaliilkreins-2

Kaliilkreins-2 (ng/ml)	Study groups	Mean	Std.	p- value
	Control	0.03	0.00	<0.001**
	Patients	0.04	0.01	

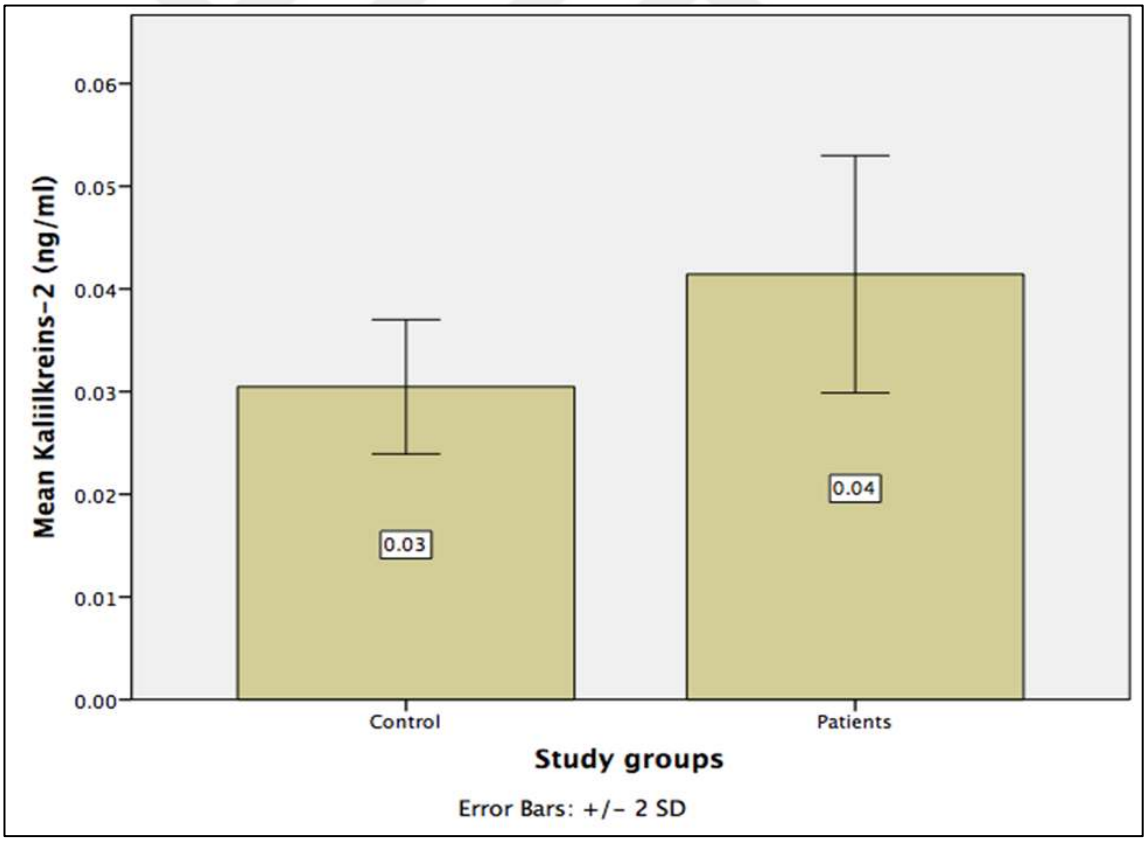

Figure 4.4 Serum concentration of Kaliilkreins-2

4.3 Biochemical Markers

4.3.1 Fasting blood sugar

Table 4.5 and Figure 4.5 show that there was a strong variation between mean of serum concentration of the total prostatic-specific antigen between the group of patients and the healthy group (1.08±0.13, 0.53±0.06 ng/ml), respectively. In addition, there was highly substantial difference between groups (p-less than 0.001**) in regard to serum concentration of TPSA.

Table 4.5 Serum concentration of fasting blood sugar

	Study groups	Mean	Std. Deviation	p- value
Fasting blood sugar (mg/dl)	Control	87.27	5.71	<0.001**
	Patients	160.00	5.63	

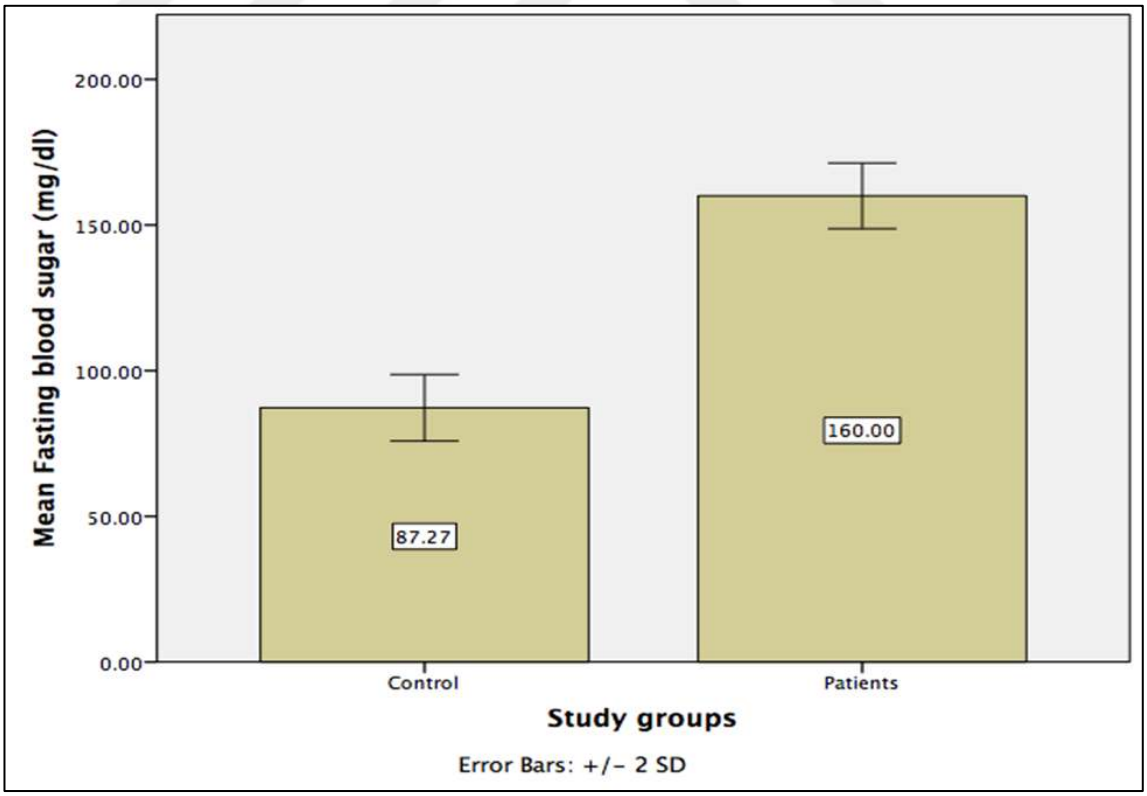

Figure 4.5 Serum concentration of fasting blood sugar

4.3.2 Cholesterol

As can be seen in Table 4.6 and Figure 4.6, there was a significant difference among the patient and the healthy groups with regard to the mean blood concentration of cholesterol (290.59 ±20.27 mg/dl vs. 173.0 ±14.63 mg/dl). In this study, the two groups' cholesterol serum concentrations were quite different from one another, with a significant (p-less than 0.001**) difference.

Table 4.6 Serum concentration of cholesterol

Cholesterol (mg/dl)	Study groups	Mean	Std.	p value
	Control	173.00	14.63	<0.001**
	Patients	290.59	20.27	

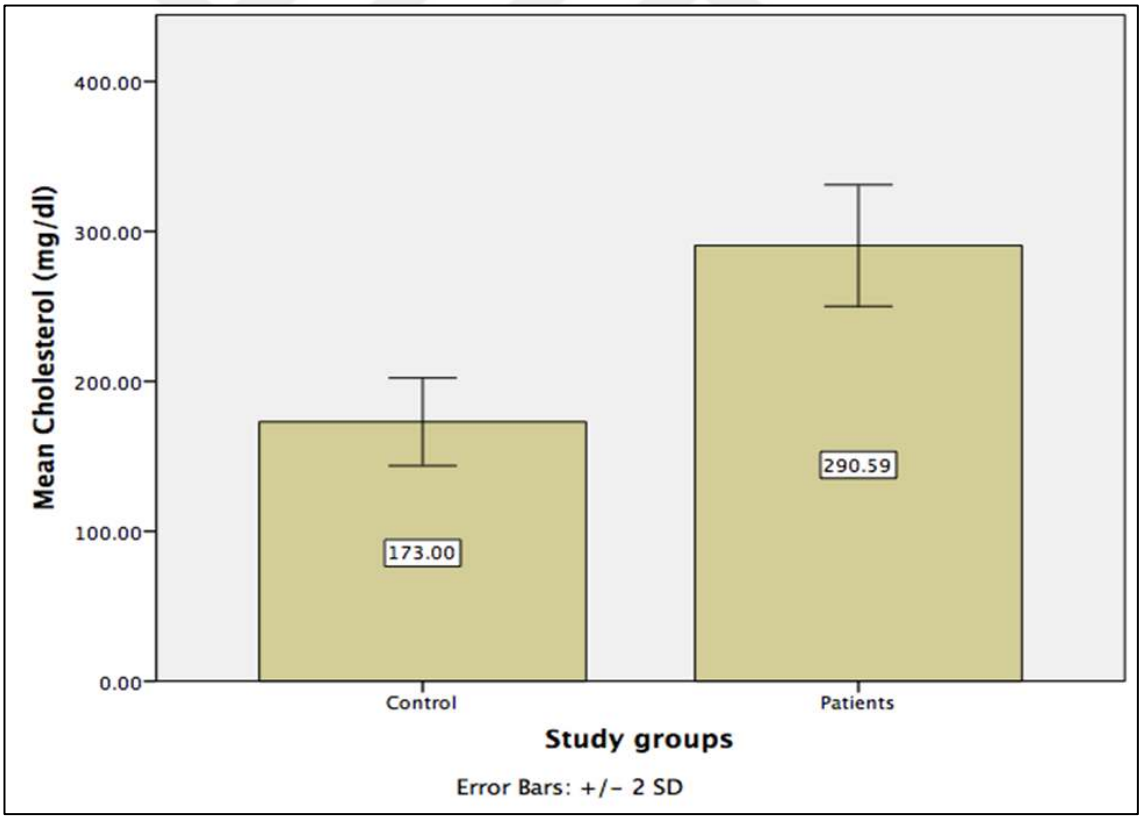

Figure 4.6 Serum concentration of cholesterol

4.3.3 Triglycerides

As shown in Table 4.7 and Figure 4.7, there was a considerable difference in mean of blood quantity of triglycerides between illness and the healthy groups (220.60±12.11 mg/dl vs. 93.68±16.72 mg/dl). In this investigation, there was a significant (p-less than 0.001**) difference between groups' blood triglyceride concentrations.

Table 4.7 Serum concentration of triglycerides

Triglyceride (mg/dl)	Study groups	Mean	Std.	p- value
	Control	93.68	16.72	<0.001**
	Patients	220.60	12.11	

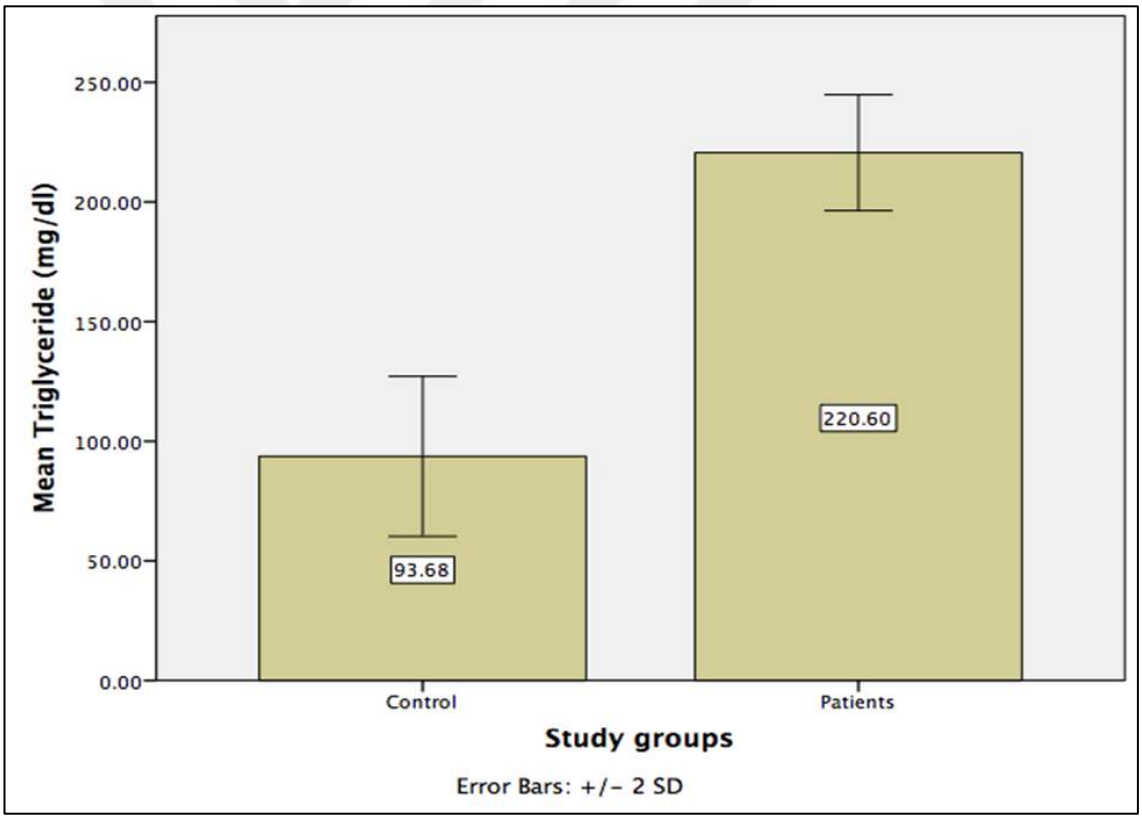

Figure 4.7 Serum concentration of triglycerides

4.3.4 High-density lipoprotein (HDL)

Table 4.8 and Figure 4.8 show that there is a high difference between the mean of serum concentration of the HDL between the group of patients and the healthy group (24.71±4.37, 39.09±6.09 mg/dl), respectively. In addition, there was significant variation between two groups (p-less than 0.001**) during the study in regard to serum concentration of HDL.

Table 4.8 Serum concentration of high-density lipoprotein

High density lipoprotein (mg/dl)	Study groups	Mean	Std. Deviation	p- value
	Control	39.09	6.09	<0.001**
	Patients	24.71	4.37	

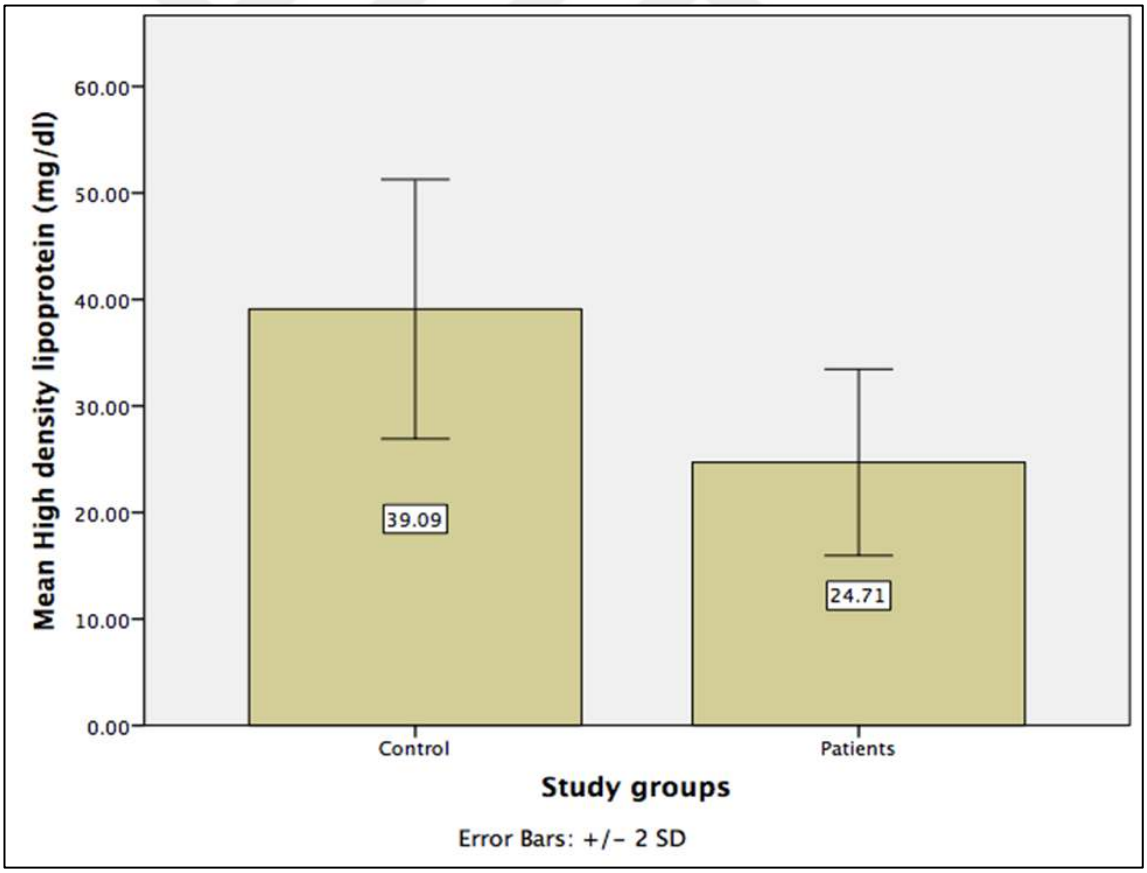

Figure 4.8 Serum concentration of high-density lipoprotein

4.3.5 Low-density lipoprotein (LDL)

There is a great disparity between mean serum concentration of LDL in the sick and the healthy groups, as shown in Table 4.9 and Figure 4.9 (221.76±19.39 mg/dl against 115.17±14.25 mg/dl, correspondingly). Furthermore, there was found a statistically considerable difference (p-<0.001**) in LDL serum concentration between the two groups in this research.

Table 4.9 Serum low-density lipoprotein concentration

Low- density lipoprotein (mg/dl)	Study groups	Mean	Std.	p- value
	Control	115.17	14.25	<0.001**
	Patients	221.76	19.39	

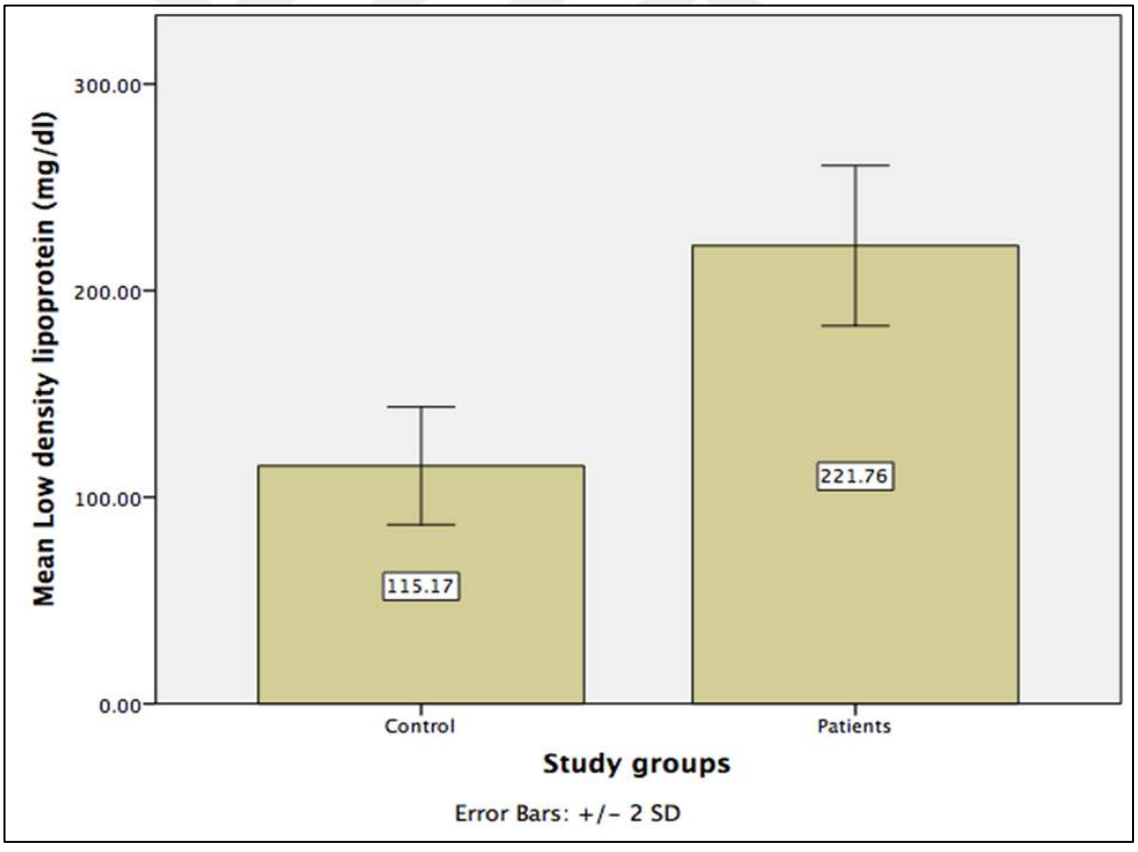

Figure 4.9 Serum concentration of low-density lipoprotein

4.3.6 Very low-density lipoprotein (VLDL)

As is apparent from Table 4.10 and Figure 4.10, the mean serum concentration of VLDL in the ill group is much higher 44.12±2.42 mg/dl than the mean serum concentration of VLDL in the healthy group, which is 18.74±3.34 mg/dl. This represents a significant difference among two groups. As well as, the VLDL serum concentration of each of the two groups in this study was shown to vary from one another in a manner that was statistically significant (p= less than 0.001**).

Table 4.10 Serum very low-density lipoprotein concentration

Very low- density lipoprotein (mg/dl)	Study	Mean	Std. Deviation	p value
	Control	18.74	3.34	<0.001**
	Patients	44.12	2.42	

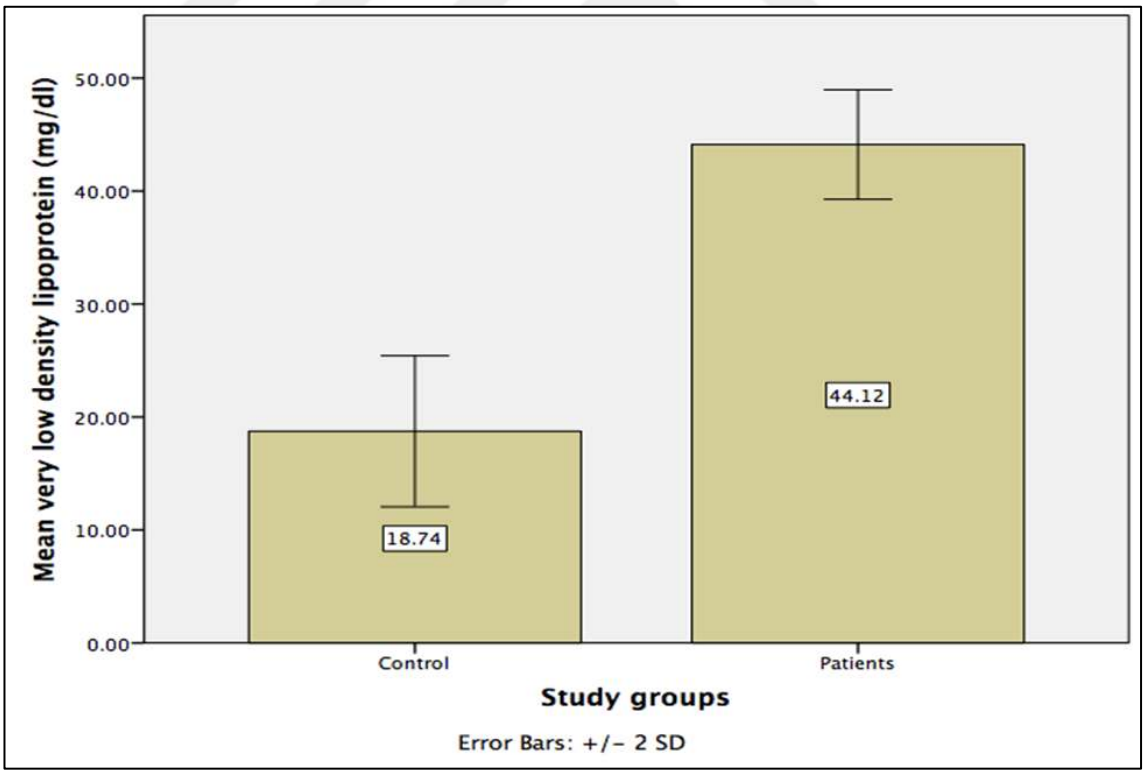

Figure 4.10 Serum very low-density lipoprotein concentration

4.4 Correlation Among Studied Markers

Table 4.11 shows that there is a positive correlation between Kaliilkreins-2 and free prostatic specific antigen. On the other hand, there were also positive correlation between levels of total cholesterol, triglycerides, LDL and VLDL in prostate cancer patients during this current study.

Table 4.11 Correlation among studied markers

Markers		Total	Free	Kaliilkrei	FBS	CHO	TG	HDL	LDL	VLDL
Total PSA (ng/ml)	r	1	0.000	-0.025	0.041	-0.149	0.104	0.175	-0.191	0.104
	p	.	0.997	0.832	0.724	0.202	0.373	0.133	0.101	0.373
Free PSA (ng/ml)	r	0.000	1	0.228*	-	0.026	0.091	0.015	0.041	0.091
	p	0.997	.	0.049	0.173	0.822	0.437	0.900	0.726	0.437
Kaliilkreins-2 (ng/ml)	r	-	.228*	1	0.008	0.128	0.136	-	0.157	0.136
	p	0.832	0.049	.	0.943	0.276	0.246	0.431	0.179	0.246
FBS (mg/dl)	r	0.041	-	0.008	1	0.215	0.106	-	0.215	0.106
	p	0.724	0.173	0.943	.	0.064	0.366	0.675	0.063	0.366
Cholesterol (mg/dl)	r	-	0.026	0.128	0.215	1	0.475**	0.085	0.952**	0.475**
	p	0.202	0.822	0.276	0.064	.	<0.001	0.469	<0.001	<0.001
Triglyceride (mg/dl)	r	0.104	0.091	0.136	0.106	0.475**	1	-	0.401**	1.000**
	p	0.373	0.437	0.246	0.366	<0.001 **	.	0.711	<0.001 **	.<0.001 **
HDL (mg/dl)	r	0.175	0.015	-0.092	-	0.085	-0.044	1	-0.149	-0.044
	p	0.133	0.900	0.431	0.675	0.469	0.711	.	0.201	0.711
LDL (mg/dl)	r	0.191	0.041	0.157	0.215	0.952**	0.401**	-	1	0.401**
	p	0.101	0.726	0.179	0.063	<0.001	<0.001	0.201	.	<0.001
VLDL (mg/dl)	r	0.104	0.091	0.136	0.106	0.475**	1.000**	-	0.401**	1
	p	0.373	0.437	0.246	0.366	<0.001	<.0.001	0.711	<0.001	.

5. DISCUSSION

5.1 Age Distribution Between Study Groups

Although traditionally thought of as a disease of older men (those aged 65 and over), more than 10% of new diagnoses of prostate cancer throughout United States are made among men under age of 55 today. Prostate cancer detected among men less than (55 years) of age is called as “early-onset prostate cancer”. This kind of the prostate cancer is distinct from the prostate cancer found in men who are older (Salinas *et al.* 2014). In this particular research, there were a total of ninety participants, who were split evenly between two groups. The first group consisted of sixty individuals who had been identifyed with the prostate cancer, while the second group served as a control group and consisted of thirty people who were healthy. The average of age of patients was over forty years old, with the control group participants having an average age of 57.13±8.76 years and the patient participants having an average age of 56.11±8.68 years. In instances when the ages of the people in the two groups did not significantly vary from one another. A second study was done in Kirkuk to find out how much PSA is in the blood. It was similar to the research that had already been done. In this particular research, there were a total of fifty-eight patients suffering from prostate cancer, fluctuating in age from (50 to 88) years, and fifty-two healthy individuals, ranging in age from fifty to eighty years. Regarding age, none of the two groups differed from the other in a way that was statistically significant (Muhammad *et al.* 2019). Another research comprised two groups of the patients, with the first group comprising of prostate cancer patients who also had diabetes mellitus and the second group consisting of prostate cancer patients who did not have diabetes. Because their ages varied from 41 to 97 years, with a mean age of 64.25 years and a standard deviation of 10.26 years, and because this research demonstrated that there was no significant variation between groups on the basis of age (Udoh *et al.* 2022). According to these findings, there are variables that can be modified and those that cannot be modified that may influence the development of prostatic cancer. These factors include age, ethnicity, family medical history, location, plus obesity, as well as disorders such as diabetes (Leitzmann and Rohrmann 2012).

5.2 Total and free prostatic- specific antigen

There is a more than twenty-five-fold variation in the prevalence rate of "prostate cancer" amongst races all around the globe. This disparity may be attributed to lifestyle as well as genetic variances. It is at its lowest point in Asia, with the exception of some countries in the Caribbean, North America, and European Countries, as well as Australia in addition to New Zealand, where it is at its highest (Park *et al.* 2018, Tan *et al.* 2017). Based to the Iraqi Oncology Institute in 2016, breast cancer had the greatest proportion of cases as well as the greatest incidence, while prostate cancer had the smallest rate. Prostate cancer was the tenth highest incidence rate among males throughout Iraq in 2016, coming in at 4.13 cases per 100,000 men (Directorate, 2016). PSA is generated by normal, hyperplastic, even cancerous prostate tissue, on the other hand, the largest quantities are discovered in the prostatic conversion phase of individuals who have benign prostatic hyperplasia (Ben Jemaa *et al.* 2010). The bulk of PSA is seen circulating within serum while coupled with protease stabilizers like "a1-antichymotrypsin and a2-macroglobulin". The residual PSA is free. When the prostate undergoes pathological changes such inflammation, hyperplasia, or neoplasia, the basement membrane becomes more permeable and more PSA is secreted into the bloodstream (Pentyala *et al.* 2016). PSA is an extremely common diagnostic tool for prostate cancer. PSA testing is more affordable than trans-rectal ultrasonography (TRUS), it can identify more prostate tumors than digitally rectal examination (DRE) or TRUS, and cancers found using PSA testing are more probable to be organ-confined than malignancies found with DRE testing alone (Catalona and Loeb 2010). Current study demonstrated that mean of serum concentration of the total and free prostatic-specific antigen between the illness group and the healthy group is markedly different. Additionally, there was highly discernible variation in the serum levels of free PSA between the two groups in this investigation (p-<0.001**). Another research, which showed results that were in accordance with ours, reported that the mean total PSA and free PSA readings of patients with prostatic cancer were significantly greater compared to patients with "benign prostatic hyperplasia" and healthy controls (Al-Dahy *et al.* 2021). These findings provided more evidence to support the findings of earlier research, which revealed that the mean serum concentrations of total and free form of

prostatic specific antigen were greater in prostatic cancer patients than the mean serum levels of the same antigens in healthy control people (Ediz *et al.* 2019). Previous research carried out by Veneziano, S., *et al.* was the foundation of the first observed relationships between total PSA with prostate volume (Veneziano *et al.* 1991). Testing for prostate cancer may lead to a marginal absolute benefit over a period of ten years for the mortality percentage of the particular illness, but it does not reduce total rates of death. The potential immediate with long-term adverse effects of the PSA detection required to be weighed against these potential positive effects. The possibility of an incorrect identification and unnecessary therapy, as well as potential consequences resulting from biopsies with the treatment that follows. The ratio of f- PSA to t-PSA was revealed to be considerably lower in cases of prostate cancer compared to benign prostatic hyperplasia (Kankonkar *et al.* 2019). Despite several investigations finding that the production of prostate-specific antigen in prostate tumor tissue reduced with rising Gleason score, the concentrations of PSA in the blood remained proportionate to the volume, Gleason score, and degree of the prostate cancer (Partin *et al.* 1997). This rise in blood PSA levels might be attributed by an elevated secretion of PSA as a result of enlarged prostatic epithelium that is disordered in higher-grade tumors (Partin *et al.* 1997).

5.3 Kaliilkreins-2

The human kallikrein-2 (hK2) serine protease is a type of serine protease that has 79 perecent of its sequence of amino acid in common with antigens specific to the prostate. In addition to this, it serves as a novel biomarker for prostatic cancer and plays a part in the diagnosis of this condition. The prostate is accountable for the creation of the vast majority of hK2, which is then secreted throughout the body in the type of proenzyme, which must then be converted into active enzymes once it leaves the cell. hK2 may be found in biological fluids such as blood, sperm, saliva, and various fluids of the body. Additionally, 80 percent to 95 percent of the hK2 that is found in the blood is in its free form. Numerous studies have shown that the blood hK2 is an effective tool for diagnosing prostate cancer and determining the patient's prognosis (Satkunasivam *et al.* 2014). Rendering to the outcomes of our investigation, there is little variation between

the groups of patients and healthy individuals with regard to the mean blood concentration of the kallikreins-2. Additionally, there was a statistically considrable gap among groups (p-values less than 0.001). Another prior research discovered that the levels of mRNA for hK2 in patients with prostate cancer were considerably greater than those in patients with benign prostatic hyperplasia (Mao *et al.* 2018). An additional investigation discovered that the mean concentration of HK2 in the blood of the patients was considerably higher than that of the normal group. Furthermore, these findings imply that early alterations, such as the marginally higher production of PSA and hK2 through the blood, suggest a tendency for prostate cancer that may be seen two decades earlier than the condition is clinically detected (Lilja *et al.* 2007). Another research looked at the expression of the gene hk2 and discovered that the level of gene expression among prostate cancer patients was significantly greater than the level of gene expression in healthy controls (Musavi *et al.* 2019). There have only been a number of research that have looked at the expression of this gene in people who have prostatic neoplasms. During 2006, study was investigated the level of hK2 expression found within prostate cancer tissue specimens and peripheral bloodstream samples. They led to the conclusion that hK2 is a more accurate indicator for prostate cancer, indicating that its expression is linked to the course of the disease (Meola *et al.* 2006).

5.4 Biochemical Markers

There is a correlation between being obese and an elevated chance of a variety of dangerous medical diseases, one of which being cancer. When it comes to prostate cancer, being overweight is linked to an increased chance of developing high-grade malignancies, which may be connected to reduced androgen levels. The fact that nations with greater dietary fat consumption also have greatest death rates of prostate cancer suggests that nutrition may possibly play a role in determining the risk of developing prostate cancer. It is noteworthy to note that prostate cancer is linked to a variety of metabolic changes, some of which have the potential to serve as useful treatment and diagnostic strategies (Ferro *et al.* 2017). The current research found that the mean serum concentration of fasting blood sugar, cholesterol, triglycerides, low-density lipoprotein, as well as very-low-density lipoprotein was clearly elevated between the

patients and healthy groups. In contrast, the mean of high-density lipoprotein was lower in patients than in healthy groups and also differed significantly (p 0.001**) between the two groups in this research according to these biochemical tests. Another Iraqi study found that patients with prostate cancer had higher levels of LDL and total cholesterol compared to normal people. However, the average levels of triglycerides and glucose in the blood while fasting were the same for both patient and control groups. HDL levels were found to be lower in patients compared to the control group (Harraz *et al.* 2019). The levels of total cholesterol, triglycerides, and LDL in addition to VLDL were found to be high in patients with prostate cancer, but the levels of HDL were found to be greater in healthy participants than they are in patients. This finding was consistent with the findings of a second research (His *et al.* 2014). The previous study found that patients with prostate cancer had significantly higher levels of cholesterol, triglycerides, low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL) compared to patients with benign prostatic hyperplasia. There was also a substantial difference between both high- and low-grade prostate gland cancer groups (Tewari *et al.* 2014). These results indicating a strong link between abnormalities in lipid and glucose metabolism and the development of prostate cancer. A crucial step in the process of metabolic remodeling is the rise in lipid production that is necessary for cellular proliferation, the development of membranes, and the transmission of cell signals. Adaptive metabolic alterations are undergone by prostate cancer cells throughout the advancement of the neoplastic process in order to maintain their proliferation and development (Lucarelli *et al.* 2015). In prostate cancer, substantial amounts of "phosphatidylcholine, phosphatidylethanolamine, as well as glycerophosphocholine" have been documented, in addition to a higher expression and function of choline kinase, an enzyme that is implicated in the manufacture of cell membrane phospholipids. These results are in agreement with mechanisms of active membrane modification as well as cellular growth. Additionally, the synthesis of lipogenesis metabolic byproducts functions as second messengers in many signaling pathways that control cell-to-cell interaction, migration, as well as invasion. The lipid metabolism phenotypes of prostate cancer are related with both the process of de novo lipogenesis as well as cholesterogenesis (Swinnen *et al.* 2004).

5.5 Correlation Among Study Variables

Further research indicates that there is not a particular biomarker that can be utilized for the diagnosis of prostate cancer (PCa). Furthermore, the use of a number of different indicators not only makes the recognize of prostate cancer more accurate but also statistically more robust. In order to get the most accurate identification of PCa possible, an unreasonable frequency of biopsies should be avoided. The current study showed that there was a positive correlation found between Kaliilkreins-2 (hK2), and free prostatic-specific antigen (fPSA). Another research looked at prostate cancer in the Syrian community and showed that the mean hK2/fPSA ratios were considerably higher in patients suffering from prostate cancer than they were in benign prostate hyperplasia patients or those in the healthy controls. In addition, the ratio of hk2/fPSA produced the highest area under the curve, which was much bigger than that produced by the ratio of fPSA to PSA. This difference is suggestive of a stronger level of specificity (Bachour *et al.* 2015). Our results are consistent with those of the research conducted by Scorilas *et al.* which found that certain kallikreins-2 are up in a variety of cancers, including, which rises in prostate cancer, and hence has the potential to serve as a biomarker for this form of the disease (Scorilas *et al.* 2003). Later, studies conducted by Martin et al as well as Nam *et al.* indicate the effectiveness of the ratio hK2/fPSA to differentiate between men with prostate cancer and men without disease, indicating that this ratio may be a valuable diagnostic function (Martin *et al.* 2004, Nam *et al.* 2000). On the other hand, our study also found that there was also a positive correlation between levels of total cholesterol, triglycerides, LDL, and VLDL in prostate cancer patients. Another research conducted in Iraq found that PC patients had considerably elevated levels of cholesterol, triglycerides, low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL), although their HDL levels were much lower than those of the controls. There was a positive correlation between and levels of cholesterol, triglycerides, low-density lipoprotein, and very low-density lipoprotein. notwithstanding the fact that there was no connection with HDL (Al-Wadi *et al.* 2022). The findings of the current research provide more evidence that there is a direct connection between blood lipid levels and the risk of prostate cancer in individuals.

6. CONCLUSIONS AND RECOMMENDATION

6.1 Conclusions

1- Among patients suffering from prostate cancer, the mean blood concentrations of total and free prostatic specific antigens was greater than in the healthy group. This finding suggests that this biomarker may play a useful role in predicting, diagnosing, and monitoring the progression of prostate cancer.

2- Prostate cancer patients had a considerably higher concentration of human kallikreins-2 than the control group did, which suggests that this protein plays a role in diagnosing the disease and determining the size of the prostate. This is especially true for patients who had a positive tissue biopsy for the disease.

3- The high levels of the lipid profile seen in patients (total cholesterol, total fat, low-density lipoprotein, and very low-density lipoprotein) and blood glucose show that obesity plays a significant role as a risk factor in the development of cancer. In addition, this surge is a strong indication that malignant disorders have an effect on the body's fat metabolism.

4- The fact that patients with prostate malignancy have been demonstrated to have a positive relationship between free prostatic specific antigen and Kallikrein-2 suggests the high level of specialization of these biomarkers in the identification of the illness.

6.2 Recommendation

1- A further investigation also required to assess the link between “prostate specific antigen (PSA)” and human kallikreins panel, histological examination, in addition to radiological screening for the identification of prostate gland cancer.

2- In order to forecast and diagnose cancer occur in prostate, students should put your attention on sophisticated and contemporary biomarkers such as metabolites, genomic and proteomic analysis as novel markers.

3- An inquiry into whether or not there is a connection between a person's family history and the lifestyle choices they make in Iraq and the increase the prostate risk to developing cancer .

4- Examining the involvement of hormones and the immune system in the development and the pathophysiology of the prostate cancer.

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