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THE RELATIONSHIP BETWEEN VITAMIN D, CALCIUM AND LIPID PROFILE DEFICIENCY WITH INFERTILITY AND THE ROLE OF THEM IN THE MEN FERTILITY

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AMMAR KHALAF FADHIL FADHIL

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May 2022

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ABSTRACT

THE RELATIONSHIP BETWEEN VITAMIN D, CALCIUM AND LIPID PROFILE DEFICIENCY WITH INFERTILITY AND THE ROLE OF THEM IN THE MEN FERTILITY

Ammar Khalaf Fadhil FADHIL

Master of Science in Chemistry

Advisor: Prof. Dr. Volkan EYÜPOĞLU

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Infertility is a term that refers to the inability to have a child after a year of marriage without using any preventive method, and couples across the world suffer from infertility. It is indicated that the causes of infertility are attributed to the male partner because of having asthenospermia, the impaired sperm motility, this leading to persistent poor motility predicts failure in fertilization. The current study included the investigation in vitro the vitamin D and lipid profile Deficiency with Infertility and their role of them in men's fertility with deficient vitamin D3 serum levels. Depending on the current result and general view according to the previous investigations and studies were unable to obtain conclusive results to establish a confidence link between vitamin D status and testis hormone production. Apart from the effects of vitamin D on sperm parameters, the majority of this research pointed to vitamin D's potential function in male reproductive health, particularly through improved sperm motility. In terms of pregnancy outcomes, a normal vitamin D level appears to be linked to a greater pregnancy rate. More research is required to further understand the particular role of vitamin D in the hormonal and seminal panel of both fertile and infertile men in the future. In this case, it becomes critical to create a specified range of circulating vitamin D serum levels in the bloodstream.

2022, 37 pages

Keywords: Men fertility, Vitamin D3, Lipids, Oligospermia, Azospermia

ÖZET

D VİTAMİNİ, KALSİYUM VE LİPİT PROFİLİ EKSİKLİĞİ İLE KISIRLIK ARASINDAKİ İLİŞKİ VE BUNLARIN ERKEK DOĞURGANLIĞINDAKİ ROLÜ

Ammar Khalaf Fadhil FADHIL

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Temmuz 2022

Kısırlık, herhangi bir önleyici yöntem kullanılmadan bir yıllık evlilikten sonra çocuk sahibi olamama anlamına gelen bir terimdir, dünya çapında çok sayıda çift kısırlıktan muzdariptir. Astenospermi ve sperm motilitesinin bozulması nedeniyle bir takım kısırlık sebeplerinin erkek partnere atfedildiği belirtilmektedir. Mevcut çalışma, vitamin D3 eksikliği serum düzeyleri olan erkeklerde in vitro D vitamini ve lipid profili Eksikliği ve Kısırlığı ve bunların doğurganlıktaki rolünü içermektedir. Mevcut sonuca ve önceki araştırma ve çalışmalara göre genel görüşe dayanarak, D vitamini durumu ile testis hormonu üretimi arasında bir güven bağlantısı kurmak için kesin sonuçlara varılamadı. D vitamininin sperm parametreleri üzerindeki etkilerinin yanı sıra, bu araştırmaların çoğu, D vitamininin erkek üreme sağlığındaki potansiyel işlevine, özellikle de sperm hareketliliğini iyileştirdiğine işaret etmiştir. Hamilelik sonuçları açısından, normal bir D vitamini seviyesinin daha yüksek bir hamilelik oranıyla bağlantılı olduğu görülmektedir. D vitamininin hem doğurgan hem de kısır erkeklerde hormonal ve seminal panel üzerindeki spesifik işlevini daha iyi anlamak için gelecekteki araştırmalara ihtiyaç vardır. Bu durumda, tanımlanmış bir dolaşımdaki D vitamini serum seviyeleri aralığı oluşturmak esastır.

2022, 37 sayfa

Anahtar Kelimeler: Erkeklerde doğurganlık, D3 Vitamini, Lipitler, Oligospermi

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Ammar Khalaf Fadhil FADHIL

Çankırı-2022

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LIST OF SYMBOLS

%	Percent
±	Plus minus
°C	Degrees Celcium
µg	Migrogram
µL	Microliter
g	Gram
h	Hour
kg	Kilogram
mg	Miligram
mL	Mililitter
rpm	Round per minute

LIST OF ABBREVIATIONS

AMH	Anti-mullerian hormone
BMI	Body mass index
C-RP	C-reactive protein
GnRH	Gonadotropin-releasing hormone
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
MRI	Magnetic resonance imaging
SHBG	Sex hormone-binding globulin
TC	Triglyceride
Tg	Thyroglobulin
UV	Ultraviolet

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1. INTRODUCTION

It is described as the inability to have a child after at least one year of marriage and without the use of any preventative methods. Infertility affects around 15 percent of all married couples across the globe. Iranian couples are more likely than the world norm to have infertility, with a frequency of 24.9 percent. According to current research, almost half of the reasons of infertility may be traced to the male spouse. One-fifth of infertile couples suffer from asthenospermia, which is characterized by decreased sperm motility. Fertilization failure is predicted by persistently low motility over the whole pregnancy (Agarwal *et al.* 2021).

Vitamin D is regarded as a critical vitamin with a wide range of physiological effects. Vitamin D insufficiency is the most prevalent nutritional deficit in the contemporary era and the most frequent nutritional shortfall in the globe. According to research, vitamin D levels in fertile males are higher than those in infertile men. According to multiple research, there is also a link between vitamin D insufficiency and poor sperm quality among infertile males who are unable to reproduce. Some research indicated that there is no clear relationship between vitamin D status and testicular hormone production. As time has progressed, it has become clear that vitamin D has more extensive effects than the conventional activities associated with bone mineralization and calcium homeostasis1. Its deficiency results in impaired reproductive performance in a variety of animal species (Al-Zohily *et al.* 2020, Sassi *et al.* 2018).

Our goal will be to explore the relationship between vitamin D and lipid profile deficiency and infertility, as well as the significance of these factors in men's fertility who have low vitamin D3 blood levels (20 ng/mL). In this research, 165 participants (55 Azospermia and 55 Olgospermia) with varied degrees of disease activity will be investigated, as well as a control group of 50 healthy people (Normalspermia) who will be matched for age, gender, and Body mass index (BMI).

2. LITERATURE REVIEW

2.1 Men Infertility

Male infertility refers to any health problem that a guy has that makes it more difficult for his female spouse to get pregnant. It is possible for male infertility to be caused by inadequate sperm production, impaired or non-functional sperm, or obstructions that prevent sperm from being delivered Krausz and Riera-Escamilla 2018). Inability to create a child may be a stressful and unpleasant experience, but there are a variety of therapies available to help men conceive a child. The male reproductive system produces microscopic cells known as sperm. Ejaculation is the process by which sperm is delivered into a woman's body during intercourse (Oud *et al.* 2019).

The male reproductive system is responsible for the production, storage, and transportation of sperm. Hormones, which are chemicals produced by your body, are in charge of this. The testicles are located in the scrotum, which is a pouch of skin located underneath the penis. As soon as the sperm exit the testicles, they are channeled into a tube that runs behind each testicle. The epididymis is the name given to this tube (Agarwal *et al.* 2021).

In the moments preceding ejaculation, the sperm are transferred from the epididymis to a second pair of tubes. The vas deferens is the name given to these tubes. Each vas deferens connects to the ejaculatory duct from the seminal vesicle at this point. When you ejaculate, the sperm combine with fluid from the prostate and seminal vesicles to form a mixture known as spermatozoa, this results in the formation of sperm, the health and unhealthy sperm are illustrated in Figure 2.1. The sperm then travels via the urethra and out of the penis to the outside world (Choy and Eisenberg 2018).

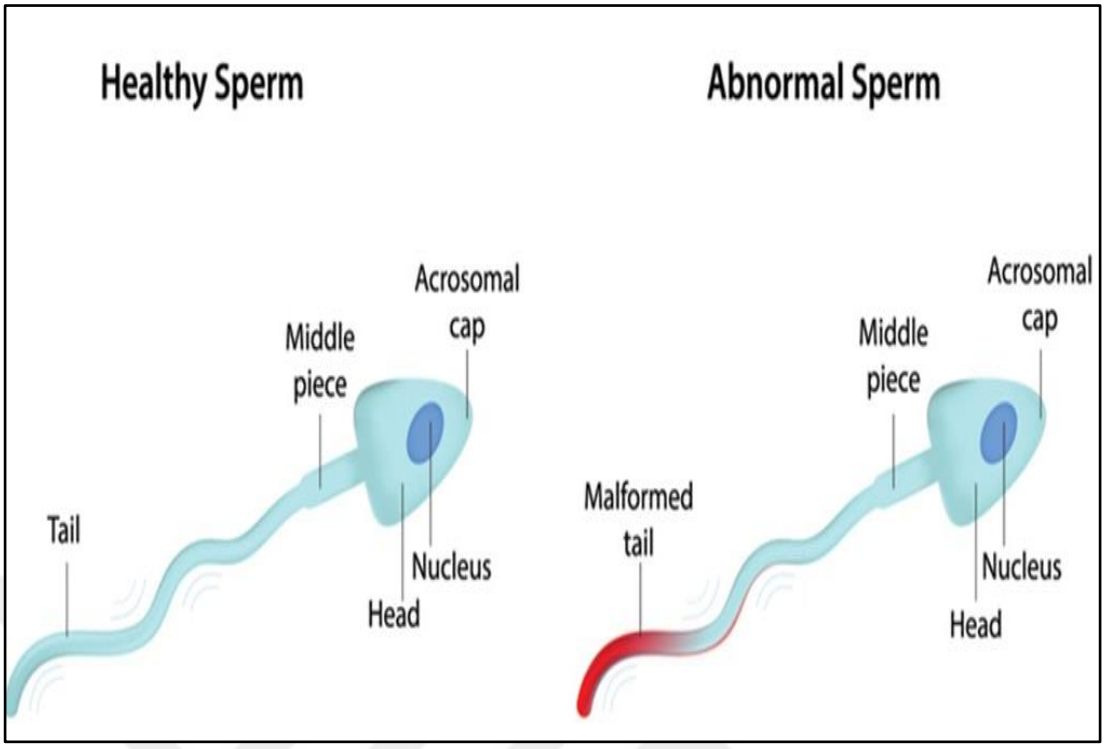

Figure 2.1 Health and unhealthy sperm (Choy and Eisenberg 2018)

Male fertility is dependent on the body's ability to produce normal sperm and transmit them. The sperm are injected into the female partner's vaginal canal. The sperm pass past her cervix and into her uterus, where they are directed to her fallopian tubes. Fertilization occurs when a sperm and an egg come into contact at this location. The system can only function properly when the appropriate genes, hormone levels, and environmental variables are present (Tournaye *et al.* 2017).

2.2 Causes of Men Infertility

Making mature, healthy sperm that is capable of traveling is dependent on a variety of factors. Problems might arise that prevent cells from developing into sperm. There are a variety of issues that might prevent the sperm from reaching the egg. Even the temperature of the scrotum has been shown to have an impact on fertility (Agarwal *et al.* 2015). Problems with sperm production might be caused by genetic characteristics. Changing one's way of life might have a negative impact on sperm count. Cigarette

smoking, alcohol use, and the use of certain drugs may all affect sperm counts (Durairajanayagam 2018).

Damage to the reproductive system might result in a poor or non-existent production of sperm. Four out of every ten men who suffer from complete loss of sperm (azoospermia) have an obstacle (blockage) inside the tubes that sperm must go through in order to reproduce. A congenital abnormality or an issue such as an infection might result in an obstruction in the flow of blood (Fainberg and Kashanian 2019).

Varicoceles are bulging veins in the scrotum that are painful to touch. Sixteen out of every hundred males are found to have them. They are more prevalent in infertile males than in non-infertile men (40 out of 100). They have a negative impact on sperm development because they obstruct adequate blood drainage. Having varicoceles increases the likelihood that blood may flow back into the scrotum from the abdomen. At this stage, the testicles become too heated to generate sperm, and the process is terminated. It is possible that this will result in a drop in sperm count (Sironen *et al.* 2020).

Retrograde ejaculation is defined as when the sperm travels backwards through the body. Instead of passing via your penis, they pass through your bladder. This occurs when the nerves and muscles in your bladder do not contract during an orgasmic experience (climax). Although the sperm in the sperm is normal, the sperm in the sperm is not discharged from the penis and hence cannot reach the vagina. Retrograde ejaculation may be induced by a variety of factors, including surgery, medicines, and neurological disorders. Cloudy urine following ejaculation, as well as less fluid or "dry" ejaculation, are signs of this condition (Babakhanzadeh *et al.* 2020).

Sometimes a man's body produces antibodies that target his own sperm, causing him to become infertile. The most common reasons for the production of antibodies are injury, surgery, and infection. They prevent sperm from migrating and performing its regular functions. There is no avaiable information about how antibodies affect fertility at this point, it seems a difficult for sperm to swim to the fallopian tube and reach an egg in certain circumstances, the probability of Causes of infertility are illustrated in Figure 2.2,

this is a rare cause of male infertility, and it should not be overlooked (Ghuman and Ramalingam 2018).

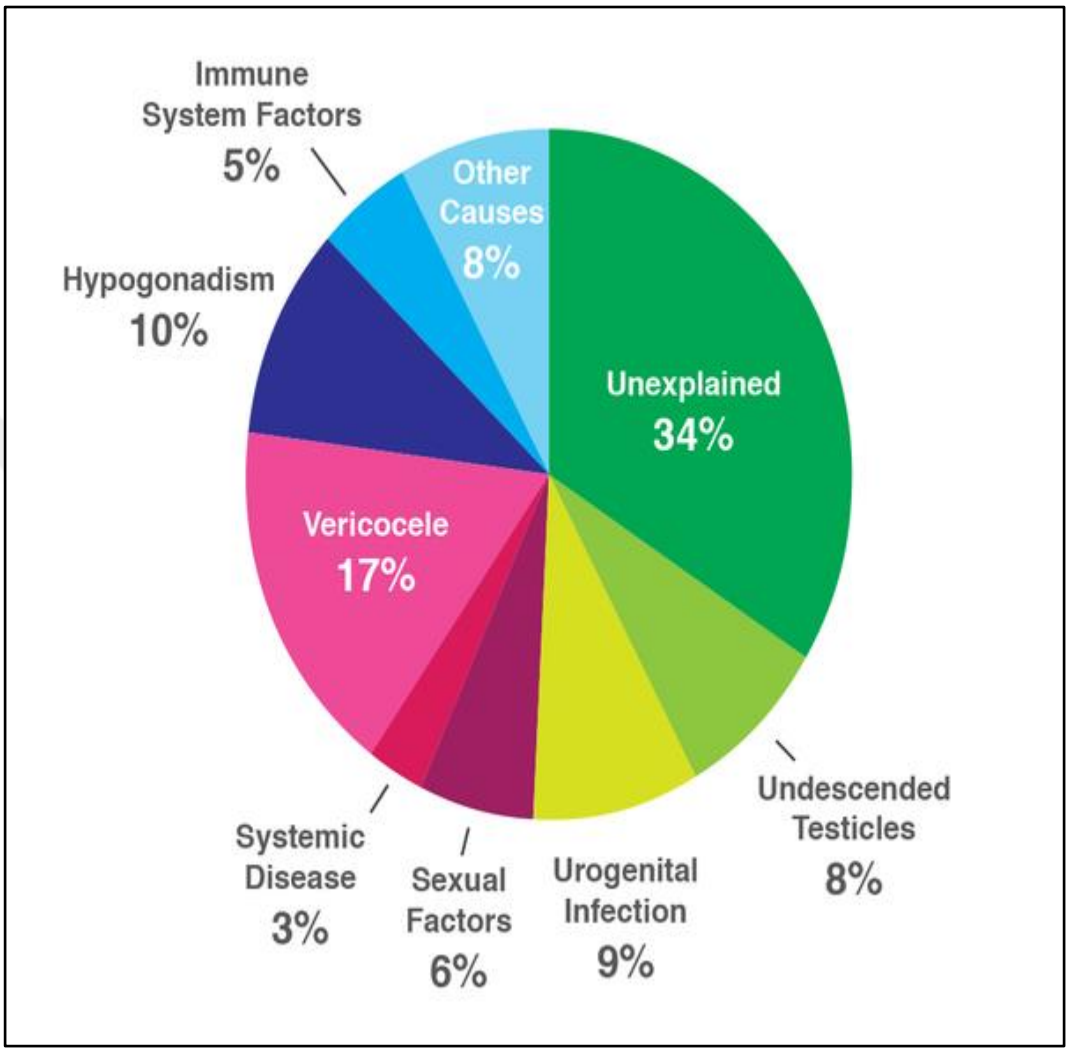

Figure 2.2 Causes of infertility (Ghuman and Ramalingam 2018)

It is possible that the channels through which sperm travels may get clogged. Infections that recur, surgery (such as a vasectomy), edema, and developmental flaws may all contribute to obstruction. It is possible to obstruct any section of the male reproductive system. A blockage prevents sperm from leaving the testicles during ejaculation, which results in infertility. The pituitary gland produces hormones that instruct the testicles to produce sperm. Hormone levels that are too low result in poor sperm development. The sperm are responsible for transporting half of the DNA to the egg. Modifications to the

number and shape of chromosomes may have an impact on fertility. For example, the Y chromosome in males may be missing portions of its DNA (Wagner *et al.* 2018).

2.1 Diagnosis of Men Infertility

Many infertile couples suffer from more than one kind of infertility, so it's possible that you and your partner will need to visit a specialist together. It may be necessary to do a variety of tests in order to discover the reason of infertility. In some circumstances, the root reason is never discovered. Infertility tests may be costly, and they may or may not be covered by insurance; check with your health insurance provider to see what is covered (Neto *et al.* 2016).

A genital examination and questioning regarding any genetic diseases, chronic health issues, illnesses, injuries, or operations that may have occurred in the past will be conducted as part of this process. It is possible that your doctor may inquire about your sexual activities as well as your sexual development throughout puberty (Barratt *et al.* 2017).

In order to get sperm samples, one may choose from a variety of options. You may deliver a sample in the doctor's office by masturbating and ejaculating into a particular container provided by the doctor. Some men choose an alternate form of sperm collecting due to religious or cultural beliefs, while others do not. When this occurs, a special condom may be used to capture the sperm over the duration of the relationship. Once your sperm has been collected, it is submitted to a laboratory for analysis to determine the amount of sperm present in the form of the sperm. In addition, the laboratory will examine your sperm for indicators of abnormalities such as infections (Agarwal *et al.* 2022). The number of sperm in a specimen might vary dramatically from one specimen to the next. Several semen analysis tests are usually performed over a period of time to guarantee that correct findings are obtained. (Harlev *et al.* 2015).

Additional tests, such as the following, may be advised to aid in the identification of the reason of infertility. Foe example, the ultrasound creates pictures in your body by using

high-frequency sound waves to transmit information to your brain. A scrotal ultrasound may assist your doctor in determining whether or not you have a varicocele or any other abnormalities with your testicles or supporting structures. In this way, your doctor may examine your prostate and check for obstructions in the tubes that transport sperm. Hormones generated by the pituitary gland, brain, and testicles are important in the development of sexual desire and the generation of sperm. It is possible that abnormalities in other hormonal or organ systems are also responsible for infertility. A blood test is used to determine the amount of testosterone and other hormones in the body. Having sperm in your urine might suggest that your sperm are moving backward into your bladder rather than out of your penis after ejaculation, which is a serious problem (retrograde ejaculation) (Leaver 2016).

When sperm concentration is exceptionally low, it is possible that a genetic factor is at play. A blood test may show whether or not there are modest alterations in the Y chromosome, which may indicate the presence of a genetic defect in the family. Various congenital or hereditary disorders may be diagnosed by genetic testing, which may be requested (Gezdirici *et al.* 2020).

A testicular biopsy is a procedure in which samples are taken from the testicles using a needle. There are a range of tests that may be used to evaluate how well your sperm survive after ejaculation, how well they can penetrate an egg, and whether or not there is any trouble bonding to the egg. These tests may not be often performed, and the results normally don't have a substantial impact on treatment recommendations (Syriou *et al.* 2018).

2.1.1 Hyperprolactinemia

Hypogonadotropic hypogonadism is a condition in which the testicles do not produce sperm as a result of inadequate stimulation by pituitary hormones. Because of a malfunction with the pituitary or hypothalamus, this occurs. It is the root cause of infertility in males in a limited proportion of cases. It may be present from birth, with symptoms often manifesting themselves when a young man is meant to go through

puberty (congenital). Alternatively, it may appear later (acquired) (Kahn and Brannigan 2017).

When the pituitary gland produces an excessive amount of the hormone prolactin, this is known as hyperprolactinemia. Infertility and erectile problems are both associated with it. Treatment is dependent on the underlying cause of the rise. If a tumor in the pituitary gland is found, it may be treated with drugs or, less often, with surgery. The congenital type, also known as Kallmann's syndrome, is characterized by low levels of gonadotropin-releasing hormone in the body from birth (GnRH). The hypothalamus is responsible for the production of GnRH. Other health concerns, such as pituitary tumors, brain trauma, and anabolic steroid usage, might cause the acquired form to manifest itself in the body (Katz *et al.* 2017).

If your health care provider suspects that you have hypogonadotropic hypogonadism, he or she may recommend that you have an MRI. This will display a photograph of your pituitary gland in a pop-up window. In addition, your prolactin levels will be checked with a blood test. Pituitary tumors may be diagnosed with an MRI scan and a blood test performed in conjunction. If your prolactin levels are high but there is no tumor on the pituitary gland, your healthcare professional may attempt to reduce your prolactin levels first. The next step would be the administration of gonadotropin replacement medication. Throughout the course of therapy, the patient's testosterone levels and sperm count will be monitored, the likelihood of becoming pregnant is really high, the sperm produced as a consequence of this therapy are healthy (Alhathal *et al.* 2020).

Some males are born with a genetic disorder that may be novel (i.e., not present in other members of the family) or inherited (i.e., handed down from mother and/or father), with the problem manifesting itself for the first time in the afflicted patient. Men with no sperm in their ejaculate (azoospermia) are most likely to have genetic abnormalities, which can be caused by a variety of factors (for example, Klinefelter syndrome, which occurs when an extra chromosome is present in the man, or Y chromosome microdeletions, which occur when a small segment of genetic tissue is missing). Genetic problems may also interfere with the development of the male tract that transports sperm, resulting in the

failure of the tubes that are meant to transport sperm from the testicles to the ovary (Katz *et al.* 2017, Herrick *et al.* 2019).

2.2 Vitamin D3

It is a fat-soluble vitamin that is found in small amounts in a few foods naturally, supplemented in others, and taken orally in supplement form. Vitamin D may also be generated endogenously when ultraviolet (UV) photons from sunshine impact the skin and encourage the creation of vitamin D in the body. In order for vitamin D to be active in the body, it must undergo two hydroxylations, which can only be accomplished by exposure to sunlight, food, or supplementation (Fetahu *et al.* 2014).

Vitamin D aids in calcium absorption in the stomach and helps to maintain normal serum calcium and phosphate levels, so supporting proper bone mineralization and avoiding hypocalcemic tetany, which are both caused by low calcium levels. Additionally, it is essential for the formation and repair of bone by osteoblasts and osteoclasts, among other things. Bones may become brittle, weak, and misshapen if they do not get enough vitamin D. Vitamin D deficiency protects both neonates and adults against the disease's rickets and osteomalacia. When combined with calcium, it can be useful in the prevention of osteoporosis in the elderly (Norman and Powell 2014).

Only a few foods contain vitamin D naturally; it is also added to others and offered as a supplement to help people get the vitamin they need. Vitamin D may also be generated endogenously when ultraviolet (UV) photons from sunshine impact the skin and encourage the creation of vitamin D in the body. In order for vitamin D to be active in the body, it must undergo two hydroxylations, which can only be accomplished by exposure to sunlight, food, or supplementation (Herrmann *et al.* 2017).

2.2.1 Vitamin D and minerals

A significant amount of 25(OH)D3 has been linked to better mineral absorption, which has been shown for calcium, magnesium, iron, phosphate, zinc, and copper, among other minerals. In addition to increased absorption of hazardous metals such as aluminum, cadmium, cobalt and lead, elevated 25(OH)D3 levels have been associated to increased absorption of radioactive isotopes such as cesium and radioactive strontium. In addition, vitamin D has been shown to help in the absorption of zinc and cadmium in chicks in studies (Amrein *et al.* 2020).

Vitamin D has no effect on mercury absorption in the chick gut, but it does boost cobalt and iron absorption in the context of low calcium levels in the diet. Increases in 25(OH)D3 levels in children during the summer months are connected with a seasonal rise in blood lead levels, which is produced by increased intestinal absorption. Also known is that the bioaccumulation of such toxic metals seems to impede the physiological function of vitamin D in the body, which is consistent with previous research. Lead or cadmium buildup, for example, might interfere with the normal production of active 1,25-dihydroxyvitamin D in the kidney. Additional research has found that numerous hazardous metals may cause a variety of negative effects on normal biological processes (Giustina *et al.* 2019). These effects can lead to health concerns. Cadmium, mercury, and aluminum are just a few of the toxic heavy metals that have been linked to adverse health effects. It has been discovered that toxic metals may build up in many bodily tissues and have been related to a variety of negative health impacts. When it comes to inorganic elements, vitamin D interacts with a wide variety of them, including both vital minerals and harmful metals (Spiro and Buttriss 2014).

The Trusted Source website states that calcium control and the maintenance of blood phosphorus levels are both dependent on vitamin D intake. These minerals are necessary for the preservation of bone health. In order for the intestines to activate and absorb calcium, as well as to recover calcium that would otherwise be expelled by the kidneys, it must be present (Chang and Lee 2019).

Deficiencies may develop over time if daily intakes fall below recommended levels, sun exposure is restricted, the kidneys are unable to convert 25(OH)D into its active form, or vitamin D absorption. Those who are lactose intolerant or xylose, as well as those who follow an ovo-vegetarian or vegan diet, are more prone than the general population to suffer from vitamin D insufficiency (Al-Zohily et al. 2020). Children with vitamin D deficiency develop rickets, a condition characterized by inadequate mineralization of bone tissue, resulting in soft bones and skeletal abnormalities. Vitamin D deficiency is associated with rickets in adults. Significant rickets may result in bone deformities and discomfort (Sassi *et al.* 2018).

2.3 Oligospermia

Oligospermia is a male infertility condition defined by a low sperm count in the male reproductive system. Other features of a man's sexual health are typical of those who suffer from this ailment. This comprises the capacity to achieve and sustain an erection, as well as the ability to generate ejaculation during an orgasmic experience (Mehta *et al.* 2015).

The number of sperm in your ejaculate might fluctuate throughout your life. In order to be fertile, a sufficient number of sperm is often required. For purposes of classification, sperm counts of 15 million or more sperm per milliliter (mL) of sperm are considered typical. Anything less than that is deemed low and is diagnosed as oligospermia or insufficient sperm production, the oligospermia types are illustrated in Figure 2.4 (Chen *et al.* 2020).

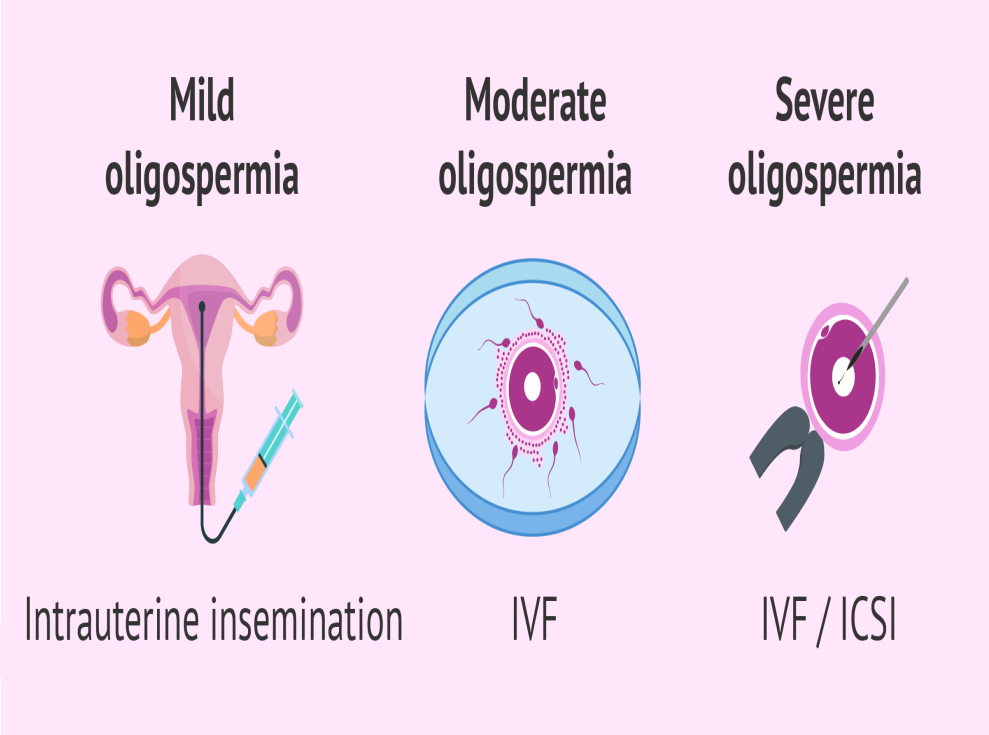

Figure 2.3 Oligospermia types (Abd- Elrazek and Ahmed-Farid 2018)

A precise number of males with low sperm counts in their sperm has not yet been determined. This is due in part to the fact that not everyone suffering from the ailment gets diagnosed. Only males who are experiencing difficulties conceiving naturally and who seek medical assistance may be diagnosed. The inability to conceive a child is the most obvious symptom of low sperm count. It is possible that there are no other evident indications or symptoms. Signs and symptoms of male infertility may be caused by an underlying issue such as an inherited chromosomal defect, a hormonal imbalance, dilated testicular veins, or a disorder that prevents sperm from passing through the testicles (Zhang *et al.* 2013).

2.3.1 Causes of oligospermia

Fertilization requires the appropriate functioning of the testicles (testes), as well as the hypothalamus and pituitary glands, which are brain structures that secrete hormone-stimulating hormones, which in turn stimulate the formation of sperm. As soon as sperm are produced in the testicles, they are transported through tiny tubes to the cervix, where

they combine with semen and are expelled through the penis (male reproductive organ). It is likely that issues with any of these systems will have an effect on sperm production (Wiehle *et al.* 2014).

An insufficient amount of sperm may be caused by a variety of health problems and medical treatments. Varicocele is one of these conditions. An abnormal enlargement of the veins that drain the testicles is referred to as a varicocele (VAR-ih-koe-seel). It's the most frequent reversible cause of male infertility, and it's also the most serious. Although the specific explanation for infertility caused by varicoceles is unclear, it is thought to be connected to aberrant testicular temperature regulation in certain cases. Varicoceles are associated with a reduction in the quality of sperm (Simmons *et al.* 2004).

Other infections may interfere with sperm production or sperm health, and some infections can induce scarring that prevents sperm from passing through the body. Ecdymitis (inflammation of the epididymis) and orchitis (inflammation of the testicles) are examples of these, as are several sexually transmitted illnesses such as gonorrhea and HIV (Cheng *et al.* 2014). Some ejaculatory issues may be resolved, but others are irreversible or permanent. It is still possible to get sperm straight from the testicles in the majority of instances with persistent ejaculatory difficulties (Azhar *et al.* 2021).

Certain surgical procedures, such as vasectomy, may result in you not having sperm in your ejaculate. In the vast majority of instances, surgery may be undertaken to either reverse or recover sperm straight from the epididymis and testicles, depending on the severity of the blockage (Azhar *et al.* 2021).

2.3.2 Effect on fertility

Despite having reduced sperm counts, some men with oligospermia are nevertheless able to conceive. Fertilization, on the other hand, may be more challenging. It may take more efforts than it would for couples who do not have a reproductive problem. It is possible that some men with oligospermia will have no difficulty conceiving despite having low sperm counts (Xie *et al.* 2018).

In addition to increasing a man's chances of developing additional reproductive problems, some of the most prevalent reasons are listed below. This covers issues related to sperm motility. A man's sperm motility refers to how many "active" sperm are present in his sperm. Normal activity makes it possible for sperm to move efficiently toward an egg in order to fertilize it. It is possible that abnormal motility means that the sperm are not moving fast enough to reach the egg. It is also possible that the sperm may migrate in an irregular fashion, preventing them from reaching the egg (Daneshmandpour *et al.* 2020).

2.4 Azoospermia

Azoospermia is a disorder in which there is no detectable sperm in a man's ejaculate, resulting in infertility (semen). Azoospermia is a condition that causes male infertility. The vas deferens are the passageway via which sperm travels from the testicles and epididymis to the cervix. The sperm is propelled forward by the constriction of the vas deferens (vaginal contraction). The seminal fluid is supplemented by secretions from the seminal vesicle, and the fluid continues to travel forward toward the urethra. Before reaching the urethra, the seminal fluid goes via the prostate gland, which mixes the sperm with a milky fluid to produce the male reproductive fluid. Finally, the semen is ejaculated (released) via the urethra, which is connected to the penis (Wosnitzer *et al.* 2014).

A normal sperm count is regarded to be 15 million or more sperm per milliliter of blood. Men who have low sperm counts (also known as oligospermia or oligospermia) have a sperm concentration of fewer than 15 million per milliliter of sperm fluid. Zoospermia is a condition in which there is no detectable sperm present in the ejaculate. Aside from consulting with a male infertility specialist, the first step would be to have a repeat semen analysis performed at a lab with a great deal of experience performing semen and sperm tests, because results can vary greatly from test to test and lab to lab due to the variability of the results. Aside from that, having a tiny quantity of sperm might radically alter the management and treatment choices available, thus obtaining accurate confirmation of the result should be the first step (Cioppi *et al.* 2021).

2.4.1 Types and causes

In addition to certain hereditary diseases such as Klinefelter's syndrome, medical therapies such as chemotherapy or radiation, recreational drugs like opiates, and structural anomalies such as varicoceles or the lack of the vas deferens on both sides are also considered possible causes. The most apparent reason for this would be a vasectomy, which stops sperm from combining with other fluids in the ejaculate and resulting in conception. However, in the majority of instances, azoospermia is most likely caused by causes that we do not completely understand, such as hereditary abnormalities, poor testicular development as a fetus or kid, or environmental contaminants (Berookhim and Schlegel 2014).

It is possible to have both Obstructive and Nonobstructive Azospermia, which are the two most common kinds. Obstructive azoospermia is a condition in which there is a blockage or a missing link in the epididymis, vas deferens, or anywhere else along the reproductive canal of a man. You are making sperm, but it is being prevented from exiting your body, resulting in no detectable quantity of sperm in your semen. You have nonobstructive azoospermia, which means you have weak or no sperm production as a result of structural or functional problems in the testicles, as well as a variety of other factors (Ghieh *et al.* 2019).

Azoospermia is identified when a sperm sample is viewed under a high-powered microscope after being spun in a centrifuge on two different occasions and no sperm is found in either of the two samples. Generally speaking, a centrifuge is a laboratory apparatus that rapidly spins a test material to separate it into its constituent components. Centrifuged seminal fluid contains sperm cells that separate from the fluid around them and may be seen under a microscope if they are there; otherwise, they are not (Vij *et al.* 2018).

3. MATERIALS AND METHODS

In order to study the relationship between vitamin D deficiency, calcium and fats with infertility and their role in male fertility, the listed devices, methods and materials were used as follows:

3.1 Material

3.1.1 Chemical material and kits

- Vit. D Kit
- Testeo Kit
- Tc Kit
- Tg Kit
- HDL Kit
- LDL Kit
- Ca Kit
- C-RP Kit

3.1.2 Devices

The devices that were present in the laboratories of the Ramadi teaching hospital for women and children were used.

- ELISA Washer
- ELISA Reader
- Spectrophotometer
- Automatic Pipette 100
- Automatic Pipette 1000
- Gel Tube
- D. Water

3.1.3 Patients groups

In this study, 140 subjects (55 Azoospermia and 55 oligospermia) with varying degrees of disease activity and a control group of 50 healthy subjects (Normalspermia) matched for age, sex and body mass index will be evaluated. The groups of the present study included below categorization, see Figure 3.1.

Group A (GA): Azospermia 45.
Group B (GB): Oligospermia 45.
Group C (GC): Normalspermia 50 (Controls group).

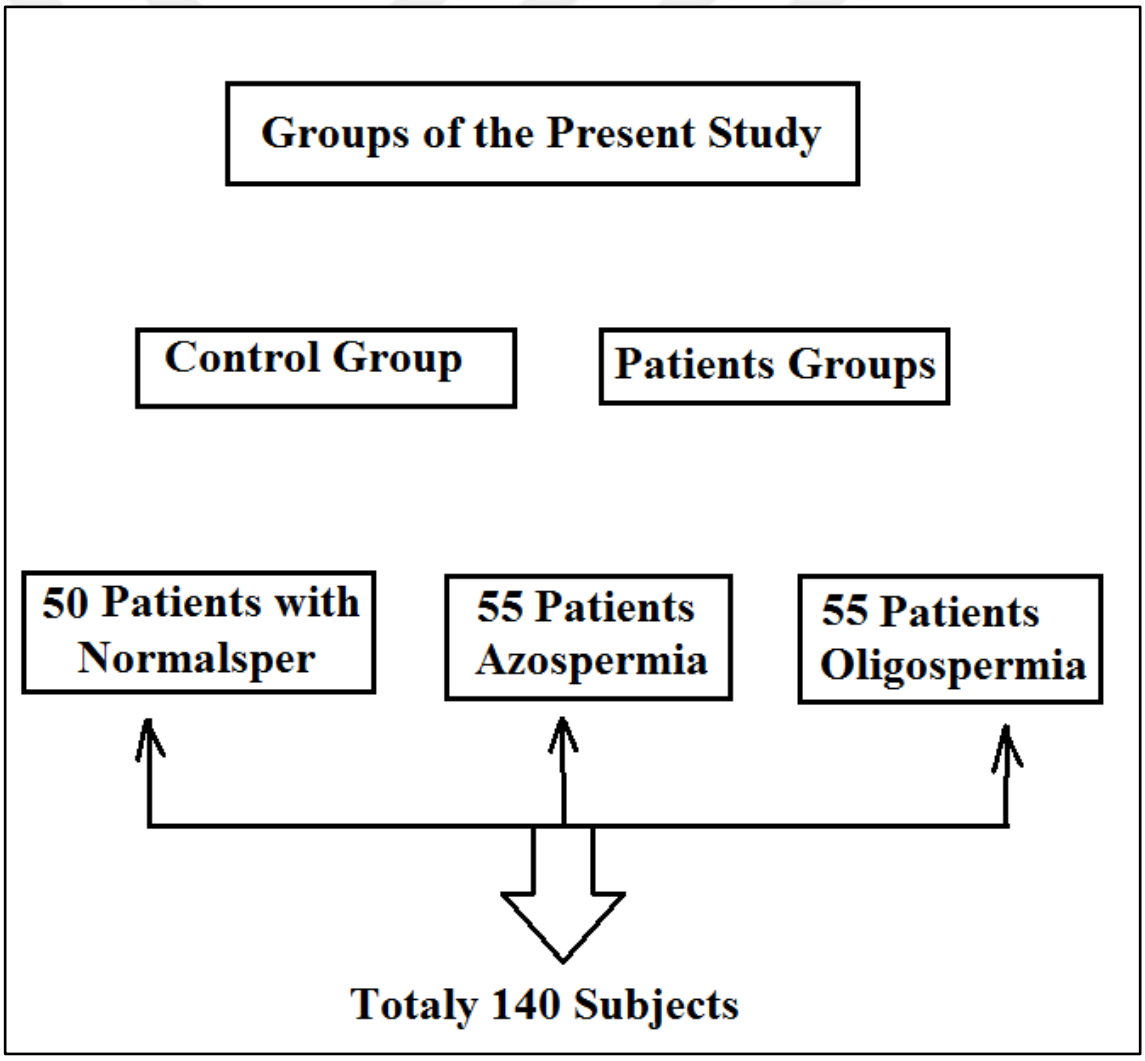

Figure 3.1 Groups of the current study

3.2 Method

Blood was drawn from patients up to 5 mL. After that, the blood was centrifuged in order to obtain the serum that will be used in the work of the chemical tests. Some tests have been done by self-devices and others have been done by semi-autonomous devices.

3.2.1 Statistc

The statistical program (SPSS 25) was used. In order to reach the results, means and Standard division the ANOVA one way test was used. We obtained correlation between groups by pearson test at P less 0.05

4. RESULTS AND DISCUSSION

4.1 Age

In this study, it is included eleven parameters, these parameters have been measured in three groups of men to discover the relationship between these parameters and fertility. The age mean and standard deviation of studied groups were (37.02 ± 8.8) and (42.96 ± 4.9) comparing with control (32.08 ± 7.3).

4.2 Weight

The weights of the studied groups were recorded as (85.96 ± 10.6) and (84.78 ± 9.5) while in control it was (84.08 ± 5.8).

4.3 Vitamine D

Vitamin D levels were recorded in infertile two groups of men as (12.5 ± 3.7) and (9.9 ± 1.8) less than in control group (19.1 ± 6.2), these results and comparsion for the description of Vitamine D have been show clearly in Table 4.1.

4.4 Testosteron

Testosteron levels were recorded in infertile for the two groups of men as (228.53 ± 52.766) and (199.18 ± 22.58) less than in control group (399±76.574), these results and comparsion for the description of testosteron have been show clearly in Table 4.1.

4.5 Tota Cholestrol (TC)

Total cholestrol levels recorded in two groups infertile men as (227.84 ± 59.082) and (262.02 ± 27.306) more than in control group (190.35 ± 23.877), these results and

comparsion for the description the levels of Total cholestrol (TC) have been show clearly in Table 4.1.

4.6 Trıglycerıde

Triglyceride levels recorded in two groups infertile men as (112.87 ± 34.882) and (125.69 ± 29.907) less than in control group (142.73 ± 30.66), these results and comparsion for the description the levels of Triglyceride (Tg) have been show clearly in Table 4.1.

4.7 Lipid Profile

High-density lipoprotein levels (HDL) recorded in two groups infertile men as (59.89 ± 13.018) and (48.24 ± 10.51) more than in control group (42.31 ± 7.498). LDL levels recorded in two groups infertile men as (145.38 ± 72.59) and (178.19 ± 34.99) less than in control group (119.49±25.72). High-density lipoprotein levels (VLDL) recorded in two groups infertile men as (22.57 ± 6.97) and (25.138 ± 5.98) less than in control group (28.547 ± 6.132), these results and comparsion for the description the levels for both HDL and VLDL have been show clearly in Table 4.1.

4.8 Calcium (Ca)

Calcium levels recorded in two groups infertile men as (8.31 ± 0.72) and (8.35 ± 0.99) less than in control group (9.49 ± 0.59), these results and comparsion for the description the levels of Calcium (Ca) have been show clearly in Table 4.1.

4.9 C-reactive Protein (C-RP)

C-reactive protein levels recorded in two groups infertile men as (8.70 ± 1.96) and (8.19 ± 2.05) less than in control group (2.15 ± 1.11), these results and comparsion for the description the levels of C-reactive protein (C-RP) have been show clearly in Table 4.1.

Table 4.1 Mean and standard deviation of studied parameters in two groups of infertil men comparing with control

Parameter	Control			Group 1			Group 2		
	Mean	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**
Age	32.08	7.345	49	37.02	8.807	45	42.96	4.913	45
Weight	84.08	5.82	49	85.96	10.604	45	84.78	9.51	45
Vit. D	19.14263	6.279947	49	12.50915	3.776333	45	9.9539	1.838554	45
Testeo	399	76.574	49	228.53	52.766	45	199.18	22.587	45
Tc	190.35	23.877	49	227.84	59.082	45	262.02	27.306	45
Tg	142.73	30.66	49	112.87	34.882	45	125.69	29.907	45
HDL	42.31	7.498	49	59.89	13.018	45	48.24	10.51	45
LDL	119.49	25.72	49	145.38	72.59	45	178.19	34.99	45
VLDL	28.547	6.132	49	22.57	6.97	45	25.138	5.98	45
Ca	9.49	0.59	49	8.31	0.72	45	8.35	0.99	45
C-RP	2.15	1.11	49	8.70	1.96	45	8.19	2.05	45

4.10 Parameter Comparison

All studied parameters were had significant differences between groups infertile men and control healthy group except the weight parameter was no significant, all these results and comparsion for the description study parameters have been show clearly in Table 4.2.

Table 4.2 Comparison between two infertile men groups with healthy control group

Parameter comparison	**Kruskal-Wallis H**	**df**	**Asymp. Sig.**
Age (year)	35.452	2	<.001
Weight (Kg)	0.149	2	0.928
Vit. D mg/dL	60.813	2	<.001
Testeo ng/dL	93.314	2	<.001
Tc	55.616	2	<.001
Tg	19.885	2	<.001
HDL	44.331	2	<.001
LDL	35.081	2	<.001
VLDL	19.885	2	<.001
Ca	38.862	2	<.001
C-RP mg/dL	94.921	2	<.001

4.11 Parameter Correlations

Weak positive correlation was noticed between Testosterone, Triglyceride, VLDL, and Ca with Vit. D. In opposite, weak negative correlation was noticed between Age, Tc, LDL, and CRP with Vit. D, all these results and comparsion for the description the study correlation have been show clearly in Table 4.3.

Table 4.3 Correlation between Vit. D level and studied parameters in two infertile men groups

Variable	Variable2	Statistic (C.I. Level: 95.0)			
		Correlation	Count	Lower C.I.	Upper C.I.
Vit. D	Age	-0.439	139	-0.564	-0.294
	Weight	-0.030	139	-0.196	0.137
	Testeo. (ng/dL)	0.471	139	0.330	0.591
	Tc	-0.408	139	-0.538	-0.259
	Tg	0.321	139	0.163	0.463
	HDL	-0.158	139	-0.316	0.009
	LDL	-0.325	139	-0.466	-0.168
	VLDL	0.321	139	0.163	0.463
	Ca	0.241	139	0.078	0.392
	CRP (mg/dL)	-0.432	139	-0.558	-0.286

4.12 Comparison with Control

Parameters that recorded more levels in control than infertile groups were Vit. D, Testo, Tg, and VLDL. While other parameters levels were recorded in control group less than in infertile groups, all these results and their comparison for the other parameters are clearly described in the Figure 4.1.

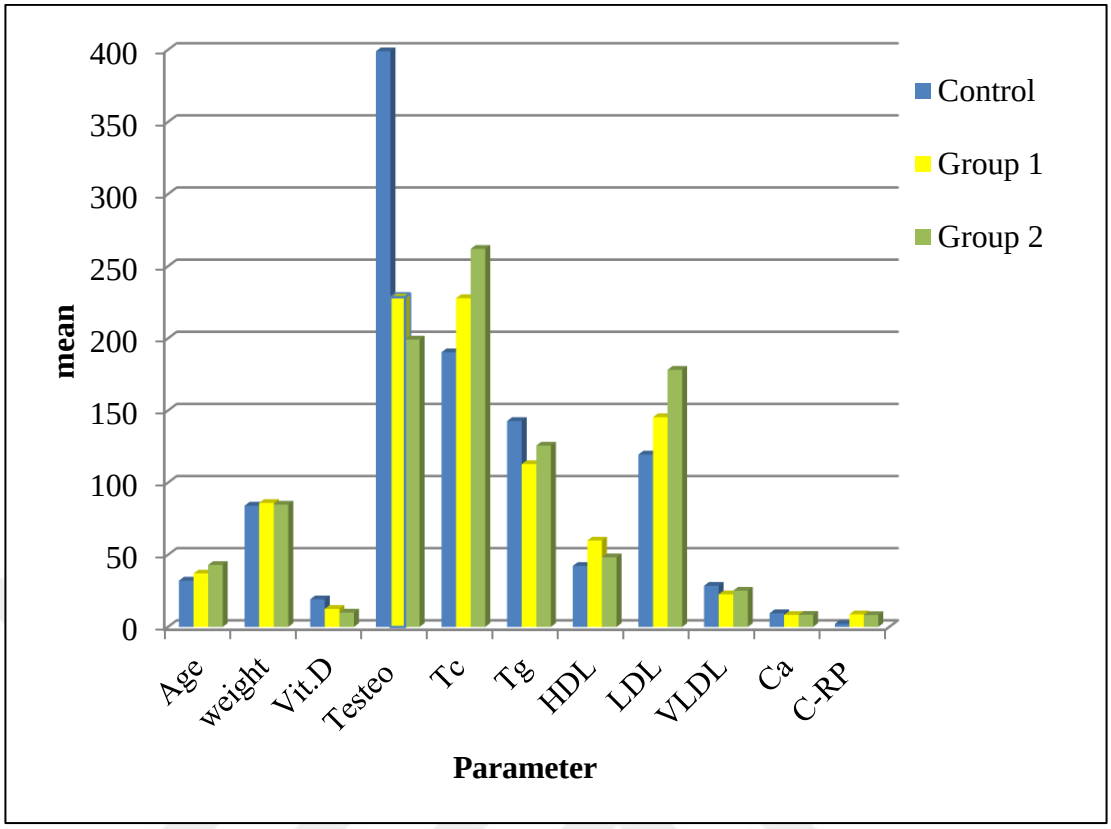

Figure 4.1 Comparison between control and infertile groups

5. DISCUSSION

Cells such as Sertoli cells, germ cells, Leyden cells, spermatozoa, and the epithelial cells lining the male reproductive canal are all known to contain vitamin D and the enzymes necessary for its metabolism. The content of vitamin D detoxifying enzymes in the external genitalia of both animals and humans demonstrates that the reproductive organs have the ability to regulate the local vitamin D response. Independent of systemic vitamin D metabolism, testicular somatic or germ cells appear to be able to produce and breakdown vitamin D locally. Furthermore, the presence of VDR in the testis shows that vitamin D may have both an autocrine and paracrine effect, possibly influencing male infertility through regulating testis activity.

The expression of VDR and vitamin D metabolizing enzymes in the male reproductive system has been widely investigated in both animal and human research. Researchers revealed that the VDR protein was present in the prostate, seminal vesicles, epididymis and germ cells, which included spermatogonia, spermatocytes, and Sertoli cells (Zanatta *et al.* 2011). Despite the fact that the VDR protein was found in animal spermatozoa, it was shown to be suppressed in the epididymis tail (Mahmoudi *et al.* 2013). The enzymes responsible for testosterone synthesis in the testicles were similarly shown to be downregulated in rats given the VDD diet (Fu *et al.* 2017). The literature (Merke *et al.* 1985) is split on the expression of VDR protein in Leyding cells, on the other hand.

Using reverse transcription polymerase chain reaction, VDR indicated a heterogeneous pattern of localization in human spermatozoa, with the postacrosome area, neck, and/or mid-piece being the most often seen locations (Blomberg Jensen *et al.* 2010).

Rat testicular RXR expression, on the other hand, has been shown in both developing and older animals (Thomas *et al.* 2011) in both developing and older animals. RXR protein was discovered in Leyding cells, Sertoli cells, and germ cells, among other places. It was discovered that the RXR protein was being produced in increasing numbers in Sertoli cells throughout the process of maturation. RXR protein is found in Sertoli cells, Leyding cells, spermatogonia, spermatocytes, and spermatids, among other cell types (Vernet *et*

al. 2006). Unfortunately, no studies have been conducted on the expression of RXR in humans. On the issue of vitamin D metabolizing enzymes, there has only been a little amount of research conducted on animals. The 25-hydroxylase and 1-hydroxylase messengers were found in the testicles of animals, while the 1-hydroxylase protein was found in the prostate, seminal vesicles, epididymis, germ cells, Sertoli cells, and Leyding cells of humans (Jensen *et al.* 2013). In a similar vein, there has been little investigation of the human male reproductive system.

It has been discovered that the function of the testicles has an impact on the effects of vitamin D on male fertility. Testicular activity is made up of two processes: hormone production and spermatogenesis, both of which contribute to male reproductive potential. According to (O'Donnell *et al.* 2017), the testis' ability to produce hormones is dependent on the existence of somatic and germ cells, both of which are essential for successful spermatogenesis. The principal hormones produced by the testis are testosterone, estradiol, anti-mullerian hormone (AMH), inhibin-B (INH-B), and insulin-like 3. The testis also produces a small amount of insulin-like 3. (INSL3). Spermatogenesis includes the processes of spermatogonia proliferation and differentiation into spermatocytes, spermatidogenesis (which includes the steps of maturation and differentiation of spermatids in mature spermatozoa), spermiogenesis (which includes the steps of maturation and differentiation of spermatids in mature spermatozoa), and spermiation (which is the release of mature spermatozoa into the lumen of the seminiferous tub Several studies have examined the paracrine and autonomic functions of intratesticular hormones.

Several research have looked into the effects of VDD on serum levels of testicular hormones, with mixed results. Furthermore, potential biases such as age, BMI, and baseline vitamin D status justified the disparities between studies. With the exception of one research (Ceglia *et al.* 2011), the majority of observational studies showed that serum levels of 25-hydroxyvitamin D3 were unrelated to circulating total or free testosterone concentrations (Chin *et al.* 2015). Furthermore, a strong association between 25-hydroxyvitamin D3 and sex hormone-binding globulin (SHBG) was discovered in some of these investigations (Välimäki *et al.* 2004). Hypovitaminosis D could, in this case,

have an indirect effect on the hormonal panel by modifying the bioavailable percentage of testosterone. On the other hand, one research that looked at the male members of infertile couples found that there was no connection between circulating 25-hydroxyvitamin D3 and total and reproductive hormone levels.

Following a recent randomized clinical study, SHBG levels and testosterone/estradiol ratios in men with 25-OHD 25 nmol/L were 15 percent and 14 percent lower, respectively, whereas free testosterone and estradiol ratios were 6 and 13 percent higher, respectively. Low Ca2+ levels were connected with a low inhibin B/FSH ratio, although a greater testosterone/estradiol ratio was shown to be associated with low Ca2+ levels (Blomberg Jensen *et al*. 2016).

But one of the factors that has sparked such a spirited discussion on this subject is that age-related comorbidities, such as endocrinology and cardiovascular disease, may affect both vitamin D measurements and testosterone levels in the bloodstream. The data for a relationship between vitamin D status and testosterone levels is presently inadequate to draw any firm conclusions.

Furthermore, studies focusing on hypogonadism patients have yielded conflicting results. Some found a link between hypogonadism and hypovitaminosis D in men with hypogonadism (Wang *et al*. 2015), whereas others found no link between hypogonadism and hypovitaminosis D in men with normogonadism (Zhao *et al*. 2017). Surprisingly, one study found a link between hypogonadism and increased vitamin D levels (Lerchbaum *et al.* 2014).

The interventional trials did not even establish a general consensus on this topic. The outcomes seemed to be highly diverse and depended on the length of vitamin D administration. It was shown that supplementation for either a short period of time (4 days) or a prolonged length of time (3 months) had no impact on total testosterone levels in the blood (Foresta *et al.* 2015). Otherwise, long-term vitamin D2 and vitamin D3 supplementation in a variety of age groups might result in a significant increase in total testosterone (Canguven *et al.* 2017), free testosterone, and SHBG (Pilz *et al.* 2011), or no

difference (Jorde *et al.* 2013). The sole study that looked at a long-term supplementation period of 24 months found no link (Ferlin *et al*. 2015). Vitamin D and testosterone production are linked by a biochemical mechanism that is currently unknown. In vitro research has shown that supplementing with vitamin D can help people feel better.

Regarding a probable link between hypovitaminosis D and estradiol levels, the majority of prior studies found no link [6061626364], one study found a positive link (Nimptsch *et al*. 2012), and one study in young infertile men found a negative link (Blomberg Jensen *et al*. 2016).

6. CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusions

Finally, all of the known observational and interventional trials yielded contradictory results. Similarly, experimental studies were unable to establish a link between vitamin D status and testis hormone production. Along with sperm parameters, the bulk of these studies indicated that vitamin D may have a role in male reproductive health, notably via increased sperm motility. In terms of pregnancy outcomes, it seems that having a normal vitamin D level is associated with a higher pregnancy rate. Research is required to further understand the particular role of vitamin D in the hormonal and seminal panel of both fertile and infertile men in the future. In this case, it becomes critical to create a specified range of circulating vitamin D serum levels in the bloodstream.

6.2 Recommendations

1- Increasing the number of selected groups as well as increasing the number of samples to reduce the standard deviation.
2- Conducting more studies and comparing them with the current study to show the impact of urbanization and the nature and type of nutrition on this type of disease.
3- Increasing the type of tests to find out other, more reliable methods of diagnosing this kind of disease

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