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Anabolic-androgenic steroids Possible Effects on Male Prostate

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Abstract: Anabolic-androgenic steroids (AASs) are testosterone analogues that have both anabolic and androgenic functions. They are used to treat variety of serious pharmaceutical conditions such as renal diseases, blood disorders, delayed puberty in men, hereditary edema, osteoporosis and growth deficiency. The prostate is the largest accessory gland in the reproductive system of male. It secretes a slightly alkaline fluid that appears to form about one third of the seminal fluid in human. The development and function of the prostate is dependent on androgens produced mainly in the testes. Anabolic androgenic steroids (AASs) users are typically in their late 20 years old to early 30 years old and most often are heterosexual males although gay/bisexual men presented extensively in the anabolic androgenic steroid community. The main reasons for administrating AASs are to increase strength and muscle mass. The majority of AAS abusers is non-competitive and appears to be driven mostly by personal goals such as achieving a more ideal body, raising performance levels, or boosting confidence. AASs are typically used in phases referred to as cycles: 'on cycles' means specific periods when the users administer AASs and 'off cycles' means an AASs -free phase. During 'on cycles' users sometimes combine different injectable and oral AASs.

Keywords: *Anabolic-androgenic steroids, Prostate*

1.Introduction

Prostate is a small walnut-sized organ that is located just below the bladder and surrounds the urethra. It is a male sex accessory gland that functions by producing and secreting fluids that contribute to the ejaculate so prostate significantly enhances male fertility [1].

Embryology and development of prostate gland: During the third month of gestation the prostate gland develops from epithelial invaginations from the posterior urogenital sinus under the influence of the underlying mesenchyme [2]. Development of prostate can occur in four stages include prostate induction which is mediated by androgen then budding of urogenital sinus epithelium (UGE) into the surrounding urogenital sinus after that ductal outgrowth that is associated with a process of branching morphogenesis, which gives rise to the mature ductal network bud and finally the solid epithelial cords undergo canalization to form the ductal lumen and cytodifferentiation to give rise to functional glandular epithelium with fully differentiated cell type [1].

During the prepubertal period, the composition of the human prostate remains more or less identical but begins to undergo morphologic changes into the adult phenotype with the onset of puberty. The gland increase continuously in size to reach the adult weight of approximately 20 g by 25–30 years of age [2].

Androgen is necessary for the prostate gland to develop normally and to preserve its anatomical and functional integrity [3].Testicular secretion is the main source of androgens, including testosterone. When androgens enter the prostatic tissue, three 5a-reductase isozymes (produced by the SRD5A1, SRD5A2, and SRD5A3 genes) change testosterone into dihydrotestosterone (DHT), which has a 30-fold higher affinity than testosterone for the androgen receptor (AR) in prostate cells [4].

During the development of prostate, verumontanum (remnant of muller duct) which originates from the endoderm of the bladder part of the urogenital sinus, has great anatomical and functional importance to which prostatic ducts from the peripheral and central zones as well as the ejaculatory ducts end on the side of it [5, 6].
Between postnatal days 15 and 30 (P15-30), the entire prostatic complex in rodents has reached its final stage of morphogenesis. maturation and growth take place throughout puberty (P25–40), when levels of circulating androgens increase [7]. In contrast, the human prostate does not grow significantly between birth and puberty, when growth starts in response to rising androgen levels. Then, it slowly increases in size over several years. While androgens drive the development and growth of the prostate, they also play a key role in maintaining a growth quiescent adult organ. It is notable that young adult males with their androgen levels are at their life peak, they do not suffer from prostatic cancer or enlargement. But, these diseases are associated with aging and a decrease in serum androgen levels [3].

Normal anatomy of the prostate The human prostate is looked like an inverted cone, with a base of 4 cm in transverse diameter, 2 cm in the anteroposterior direction, and 3 cm in its vertical diameters. It is traversed in its vertical axis by the urethra and in a more horizontal and posterior plane by the ejaculatory ducts [8]. The bladder neck serves as the prostate's base and the urogenital diaphragm serves as its apex. The prostate and seminal vesicles are posteriorly separated from the rectum by the Denonvilliers' fascia which is thin, filmy layer of connective tissue [9]. The human prostate is weighing around 2 g in childhood. At puberty it go through a phase of exponential growth, increasing in size to about 20 g. This is related to increase in serum testosterone level to adult levels. Mean prostatic weight then steadies and remains properly constant until the third decade of life when mean prostatic weight begins to incease slowly. This increase reflects the onset of pathogenesis of benign prostatic hyperplasia [4].

Guerra et al. [10] stated that the periprostatic tissue comprises adipose tissue, small blood vessels, lymphatics, the periprostatic fascia, the posterior prostatic fascia, and seminal vesicles fascia and other structural ligaments that hold the prostate.
The human prostate is composed of glandular and stromal elements, tightly fused within a pseudocapsule. The inner layer of the prostate capsule is composed of smooth muscle with an outer layer covering of collagen. There are two anatomic defects in the prostatic capsule: at the apex (anterior and anterolaterally) and at the site of entry of the ejaculatory ducts. In these areas, it can be challenging to determine the pathologic stage of adenocarcinoma of the prostate [2].
Lobar concept of intraprostatic anatomy
The first detailed description of the anatomy of the prostate is that reported by Lowsley [11]. This traditional concept divided the prostate into lobes: an anterior, middle, posterior and two lateral lobes. For about 60 years, This method has been used to identify the prostate and prostatic disease cited in Chen et al [12].

The anterior lobe was located from the anterior boundary of the gland to the level of the prostatic urethra.The middle lobe was a small region between the proximal prostatic urethra and the ejaculatory ducts. This lobe extnds from the base of the prostate to the level of verumontanum. The posterior lobe was located posterior to the ejaculatory ducts and extends to the posterior margin of the gland. The two lateral lobes extend from the lateral margin of the gland bilaterally toward the middle region of the gland. None of these lobes has clearly defined medial margin [13].

The zonal concept of intraprostate anatomy Then, the nomenclature that is most commonly used to describe the human prostate structure is that reported by McNeal [14]. He divided the prostate into several zones around the urethra that are histologically distinct and anatomically separate (Diagram I). These areas are three glandular regions termed peripheral, central and transitional zones which contain a complex separate ductal system and the non-glandular fibromuscular stroma [15].

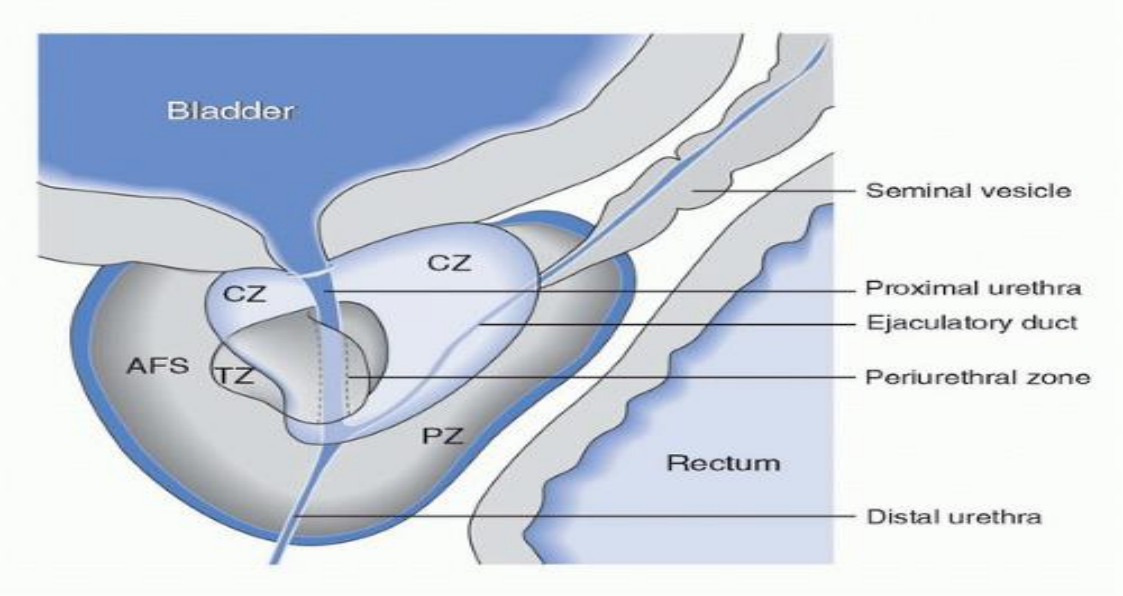

Diagram I.A natomic zones of adult prostate gland. CZ is central zone, PZ is peripheral zone, TZ is transitional zone and AFS is anterior fibrous stroma [15].

The peripheral zone (PZ) is the largest glandular zones that forms about 70% of the prostatic glandular tissue and is the site for about 70% of prostate cancers. It surrounds the distal urethral segment and is separated from the transition zone and central zone by the surgical capsule. Peripheral zone ducts emerge into prostatic urethra distal to verumontanum. While, the central zone(CZ)which is wedge shaped at the prostate base between the peripheral and transition zones forms 25% of the glandular tissue. This zone is the site of origin of only about 5% of prostate cancer so it is thought to be relatively resistant to disease processes. While, transition zone (TZ) contains approximately 5% of the prostatic glandular tissue and it is seen as two small glandular areas situated like saddlebags nearby to the proximal urethral sphincter. It is the site of origin of most benign prostatic hypertrophy (BPH) and about 20% of prostate duct cancer [2].
The anterior fibromuscular stroma (AFM) represents the convexity of the anterior external surface. The apical part of this area is rich in striated muscle, which merge into the gland and the muscle of the pelvic diaphragm .While the base is formed of smooth muscle cells which merge into the fibers of the bladder neck. The proximal section of the AFMS is crucial for involuntary sphincter functions, whereas the distal portion is significant for voluntary sphincter functions [16].

A comparison of Lowsley lobar and McNeal zonal concepts of anatomy is possible and important to compare the clinical findings.Clinicians may still refer to lobar anatomy while radiologists use zonal anatomy.So, the

anterior lobe correlates with the anterior fibromuscular stroma. The medial lobe and the central zone are the same. Both posterior and the two lateral lobes correlated to a large extent with the peripheral zone [17].

The prostate gross structure differs considerably between species. Interest in its biology is centered on the human organ and that of the species, notably rats and mice, used as a model for human diseases. A clear understanding of the differences in its structure of human and rodent is important in assessing the results of animal studies [3].

The prostate in rats is an organ with four lobes arranged circumferentially around the urethra, not a single compact anatomical structure as in human. The ventral, lateral, dorsal, and anterior lobes are the names of these lobes, which are named according their spatial orientation. Prostate in rat is located anterior to the urethra and caudal to the bladder [18]. The ventral prostate (VP) can be recognized as a gelatinous pinkish mass that partially encircles the urethra ventrally. The ventral prostate is bordered by two lobes that lay on both sides of the urethra to form the lateral prostate (LP). The butterfly-shape dorsal prostate (DP) is situated bilaterally at the base of the seminal vesicles is located dorsolateral to the bladder. Lateral prostate and dorsal prostate together are often named as the dorsolateral prostate (DLP). The anterior prostate lobes (AP) which are identified as "coagulating glands", are glowing and bilaterally attached to the lesser curvature of the seminal vesicles. The human prostate is anchored to the bladder pelvic floor and in front of the rectum. However, each of the distal ends of the rat prostate lobes floats freely in the pelvic cavity [19] (diagramII)

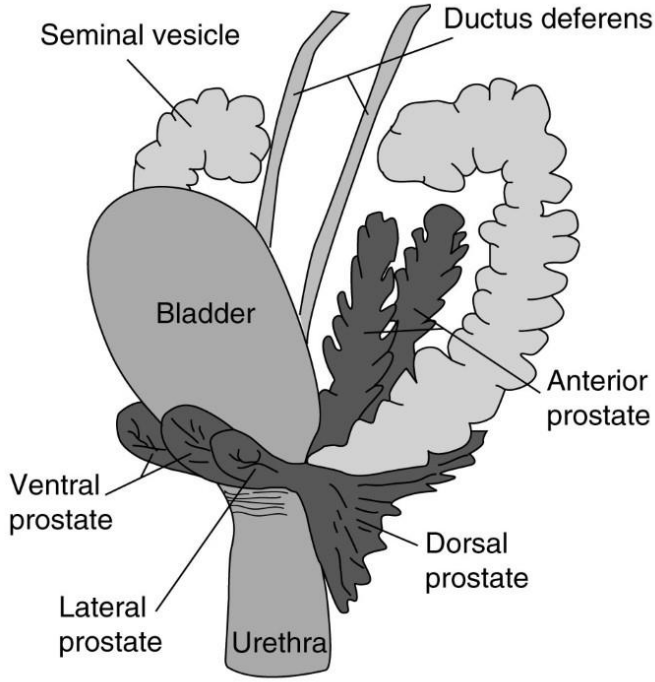

Diagram II. Schematic illustration of mouse prostate showing different lobes of the prostate and their relation to adjacent structures

Histology of prostate gland

The general histological structure of prostate is common to all the rodents and human. The most obvious difference between the prostate of both species lies in the stromal com¬ponent, which is very well developed in humans in the form of an anterior fibromuscular region. However, In rodents it is scant with min¬imal smooth muscle cells. Furthermore, there is a ratio of 1:1 basal to luminal cells in the human prostate, but in rat and mouse is nearly 1:7 [20].

Histologically, Each lobe of prostate is made up of distinct glands (alveoli or acini) and a network of branching ducts that drain individually into the urethra. The acini are separated by a thin loose connective tissue that contains stromal cells, interposed smooth muscle cells, vessels, nerves, ganglia, macrophages, and mast cells

[21].

Prostate consists of 30 to 50 tubuloalveolar glands arranged in three concentric layers: an inner mucosal layer, an intermediate submucosal layer, and a peripheral layer containing the main prostatic glands. The glands of the mucosal layer secrete directly into the urethra while the other two layers have ducts that open into the prostatic sinuses located on either side of the urethral crest on the posterior wall of the urethra [22].

The human and rodent prostate are anatomically distinct.However, they are very similar at the cellular level which consists of acini and ducts with similar epithelial cell types that include principal luminal cells, basal cells (less abundant and in discontinuous layers in mice), and neuroendocrine cells (Diagram III) [23]. The acini have an undulating to papillary appearance in most cases . This papillary configuration is markedly more obvious in the central zone [24].

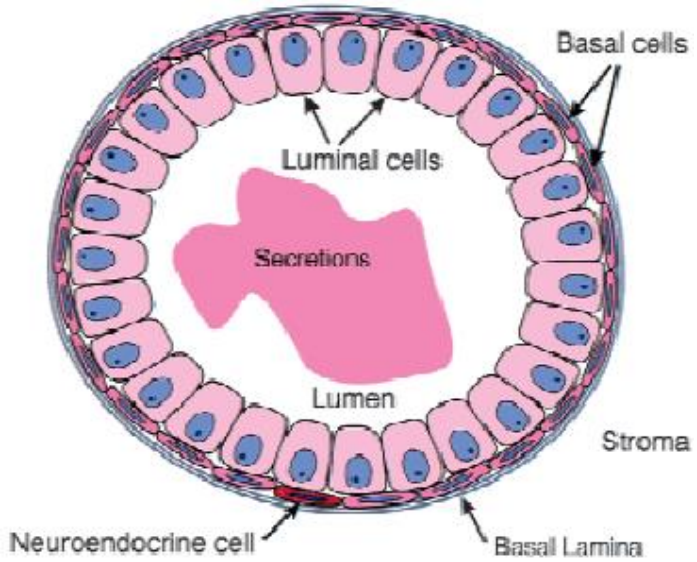

Diagram III The location of luminal secretory, basal and neuroendocrine cells are shown adapted from [24].

Principal cells (Luminal cells) are large columnar secretory cells measuring about 12um in height. Multiple microvilli are present on the luminal surfaces of these cells. Nucleus of principal cell is situated in lower third of cell and it displays discrete chromatin and prominent nucleolus. Small dispersed mitochondria, a moderately developed Golgi apparatus, long anastomosing cisternae of rough endoplasmic reticulum, several lysosomes, few lipid droplets and glycogen particles can all be seen in the cell's cytoplasm. Supranuclear and apical cell portions of the cytoplasm are filled with unit membrane-bound secretory vesicles of extreme polymorphism; some appear empty while, others display a fine granular material. Secretory vesicles discharge its contents via exocytosis [25].

Basal cells are markedly flattened cells that run parallel to the underlying basement membrane. they are characterized by slender dark nuclei and minimal cytoplasm. They are considered to be the pluripotent stem cells that capable of differentiating into luminal secretory and neuroendocrine cells . Basal cells can go through myoepithelial metaplasia, but they are not myoepithelial cells, since they lack muscle filaments as demonstrated by electron microscopy [26].

Neuroendocrine (NE) cells are difficult to be identified under light microscope but they can be seen by electron microscopy because they have elongated cell bodies and cytoplasmic dense core secretory granules. They produce a variety of neurosecretory products with growth-promoting activities in order to maintain homeostasis in the prostate. Immunohistochemistry (IHC) which uses antibodies against markers of neuroendocrine differentiation such chromogranin A (CgA), synaptophysin (SYN), and neuron-specific enolase (NSE), is a considerably more useful technique for highlighting neuroendocrine cells in human prostate tissue [27].Electron microscopy can distinguish between the open-type and closed-type of NE cells. Long microvilli that extend into the lumen of open-type cells allow them to sense pH changes and react to other chemical

stimuli in luminal secretions. Closed-type cells have dendritic-like processes and receive stimuli from smooth muscle cells, blood arteries, and nerve endings [28].

Each of the rat prostate lobes has unique histology, and can be visualized under the microscope according to their location in relation to the urethra and seminal vesicles. The dorsal prostate (DP) lobes are made up of acini that are smaller in diameter than the other lobes, lined with columnar epithelium with moderate infolding and sporadic tufting, and encircled by a relatively dense stroma. their cytoplasm is lightly eosinophilic and granular. The luminal secretion is homogenous and eosinophilic [19].These lobes are the major sites of fructose secretion [29].

The lateral lobes(LP) are made up of a flat luminal surface lined by cuboidal to low columnar epithelial cells that form scanty infoldings. The glandular lumen is of differet sizes from small to large and contains eosinophilic secretion. the lateral lobe's secretory cells have small nuclei that are situated basally within an eosinophilic cytoplasm that is less granular than that of the dorsal prostate [21].The anterior prostate(AP) or coagulating gland is distinguished by complex acini that show typical papillary or cribriform patterns. The luminal space is lined by cuboidal to columnar epithelial cells, and is filled with copious homogenous eosinophilic secretion. The nuclei of the epithelial cells of anterior prostate are centrally located within an eosinophilic granular cytoplasm, and nucleolus is small or inconspicuous. Each of the glands is usually surrounded by a prominent fibromuscular layer [19]. The ventral one is made up of densely packed, variable sized acini that are lined by low to tall columnar epithelium, basophilic cytoplasm, a nucleus that is basally situated, and a supranuclear clear region. With very little smooth muscle around them and pale eosinophilic serous or flocculent discharges, glands exhibit very little infolding [21].

The prostate is the major male reproductive gland involved in male fertility. Indeed, male fertility intrinsically relies upon the content of the prostatic fluid secreted by the prostate epithelium. The key contribution of the prostatic fluid to male fertility is linked to its role as the trigger for each of the molecular pathways involved in ejaculation and, subsequently, in sperm activation and capacitation [30, 31].

The function of the prostate relies on its composition of both glandular and fibromuscular tissue. The fibromuscular tissue aids in the compartmentalization of fluids during urination and ejaculation. During urination, the central zone muscles contract so preventing urine from entering prostatic ducts. During ejaculation, the muscles near the top of the prostate, surrounding the base of the bladder, contract to prevent back-flow of semen into the bladder. The glandular tissue contributes a reproductive function through its significant secretory contribution to seminal fluid, including both ions (notably zinc and citrate) and proteins such as prostatic acid phosphatase (PAcP), microseminoprotein, and prostate-speicific antigen (PSA) [32]. Prostatic fluid constitutes approximately one-fifth to one-third of the volume of the entire ejaculate [31, 33].

The normal human prostate accumulates the highest levels of Zn2+ more than any soft tissue in the human body [34]. This unique property relies on the fact that prostatic epithelial cells accumulate Zn2+ by an androgen-dependent Zn2+ cellular uptake and release cycle that is mediated by specific zinc transporters [35]. Once the ejaculation cue is triggered, the sperm-enriched epididymal fluid is mixed with both prostatic fluid enriched with Zn2+, citrate and PSA and with semenogelin-containing seminal vesicle secretions, which together form the bulk of the semen [34].

Prostatic secretion has an alkaline pH (7.2–8.0) from seminal containing basic polyamines such as spermine, spermidine, and putrescine, which counteract the vaginal acidity and are important for sperm survival [36]. In addition, this alkaline fluid contain coagulation factors, such as fibrinogen, factor XIII and thrombin, are present in semen and are responsible for the formation of a clot after ejaculation. This clotting of the semen helps to keep the spermatozoa in the female reproductive tract, preventing their premature expulsion . After some time, the clot is broken down by the enzyme fibrinolysin, which is also present in semen, leading to the liquefaction of semen. This liquefaction allows the spermatozoa to move freely in the female reproductive tract, facilitating fertilization [37].

Another function of prostate is releasing prostasomes which are secreted from the acinar lumen of prostate epithelial cells and mixed with semen during or after ejaculation [38]. Prostasomes are highly rich in cholesterol, which is very unusual compared to any other cholesterol rich membranes found in other body fluids [39]. Sphingomyelin is the major component of prostasome membrane and believed to protect prostasomes against any membrane attack by reactive oxygen species. and are rich in many important proteins, lipids, many small molecules, ions .Prostasomes involvement in fertility starts from its fusion with sperm cells followed by transport of important proteins and lipids from its membrane to sperm cells. The fusion of prostasomes and sperm cells has many functions such as enhancement in motility [40] promoting acrosome reaction , sperm capacitation , immunomodulation of female reproductive tract , coagulation activity ,antibacterial activity, antiviral activity and many complementary regulation [41].

Corpora amylacea (CAM) are frequent luminal contents of prostatic acini and appear to increase with patient age. They vary in size from very tiny up to a few millimeters in diameter,their shape may be round, triangular, or irregular, and their color may be pink-purple or orange-brown, but they are typically pink and round with concentric laminations. They also correlate with prostatic calculi. CAM are frequently observed in association with damaged epithelium, gland atrophy, and gland occlusion, with adjacent areas of chronic or acute inflammation [42].

Similar to the blood-brain barrier, the blood-prostate barrier protects the prostate tissue and has the function of permselectivity. In multicellular organisms, tight junctions (TJs) are intercellular junctions adjacent to the apical end of the lateral membrane surface that prevent drug from being fully enter the prostate tissue, which limits the efficiency of the treatment [43].

Despite , androgens are essential for the regulation of prostate growth and functions, intra-prostatic metabolism of testosterone to estrogens has been proposed to play a vital role in the regulation of prostate gland growth . The identification and localization of estrogen receptor β (ERβ) in the prostate gland suggested that locally produced testosterone metabolites with estrogenic activity may serve to balance the androgenic action in this tissue. In physiological conditions, estrogen signaling driven by ERβ has been shown to negatively regulate prostate gland growth [44].

Estrogens are a family of sex hormones including estrone (E1), estradiol (E2), and estriol (E3), which have a carbon ring structure derived from cholesterol biosynthesis. These compounds easily cross hydrophobic cell membranes and perform their action via binding to membrane-associated receptors and estrogen receptors that localize to the nucleus triggering changes in gene transcription and expression in various organ systems [45]. ERs are present throughout the body, and serve a number of functions in the cardiovascular, musculoskeletal, immune, and central nervous systems. The most extensively studied ERs are estrogen receptor alpha (ER-α) and beta (ER-β). Studies suggest ER-α has a proliferative effect on cell tissue, while ER-β has an anti-proliferative effect, suggesting that ERs are critical for the development of several organs including the uterus, ovary, mammary gland, prostate, lung, and brain [46, 47]. The competing nature of these receptors has been demonstrated that in rats treated with ER-α agonists,the use of ER- β agonists appeared to prevent the development of prostatic intraepithelial neoplasia (PIN), a precursor lesion in the development of cancer prostate [45].

Prostate-specifi c antigen (PSA), a 33 kDa serine protease, is one of the most clinically important tumor markers. In normal conditions, PSA is secreted into prostatic gland alveoli and ultimately incorporated into seminal fluid. The alveolar secretion from the prostate gland is pumped into the prostatic urethra during ejaculation by contraction of the fibromuscular tissue of the prostate. Because PSA is predominately released into prostatic secretion, only a very small amount of PSA is circulating in the blood of a healthy individual. However, in prostate cancer, serum concentration of PSA increases; large amounts of PSA are produced and misdirected into the circulation by the transformed prostatic epithelium. Therefore, the elevated levels of PSA are directly related to increased activity of the prostatic cancer cells. A PSA level between 4 and 10 ng/mL suggests about 25% percent cancer risk; levels above 10 ng/mL suggest a risk greater than 67%. An increased PSA serum level is used as clinical marker for the presence and progression of the diseas [22].

Anabolic androgenic steroids (AAS) are known for their anabolic and androgenic effects [15]. They represent a large group of synthetic substances that imitate the actions of testosterone which is the male sex hormone. Bodybuilders and other athletes use these substances to gain more muscle mass, strength, and energy as well as to reduce recovery times after exercise [48].

Pomara et al. [17] reported that AASs are now divided into three main groups according to how the base molecule is substituted. Class I is related to carbon C-17 esterification. Class II is related to a demethylated group at carbon C-19 and may also have carbon C-17 esters. Class III is related to alkylation at carbon C-17. (Table1)

Class Chem0ical Structure Examples

I Testosterone propionate

II Nandrolone decanoate

III Stanozolol

Table 1. Classification of anabolic androgenic steroids (AAS) [49]

The anabolic androgenic effects of AAS are performed by the androgen receptor (AR)-signaling action. Androgen receptors are extensive in human tissues and organs. There are three main action mechanisms; either by direct binding to androgen receptor or via dihydrotestosterone (DHT) produced by the action of 5- a-reductase or via estrogen receptors by a way of estradiol produced by cytochrome P(CYP19) aromatase. In particular, free testosterone is conveyed into target tissue cell cytoplasm, binding to the AR occur either directly or after conversion to 5αdihydrotestosterone (DHT) by the cytoplasmic enzyme 5-alpha reductase. Inside the cell nucleus, both free or bound testosterone binds specific nucleotide sequences of the chromosomal DNA. The produced DNA activate the transcription of specific responsive genes, with major influence on protein synthesis [50].

The history of anabolic androgenic steroids (AASs) is an exciting story that has its origins in prehistoric endocrinology.Farmers found enhanced domestication of animals after castration more than 6000 years ago .In 1889, French physiologist Charles Edouard Brown-Sequard stated that an extract of guinea pig and dog testicles given intravenous (i.v) results in an increase in physical activity, improvement in intellectual energy and relief of constipation. In the late 1930s the anabolic androgens were isolated. In 1940s, starting the use of supraphysiological doses of AAS in eugonadal individuals for anabolic benefit and scientists confirmed that androgens, particularly testosterone, could facilitate muscle growth [51].

Mullen et al. [20] mentioned that Anabolic androgenic steroids (AASs) users are typically in their late 20 years old to early 30 years old and most often are heterosexual males although gay/bisexual men presented extensively in the anabolic androgenic steroid community. Females also use anabolic androgenic steroids but at lesser extent.

The primary target tissue for the anabolic actions of AASs are skeletal muscle, their actions are mediated by androgen receptors (AR) which are up-regulated and their number has increased after administration of AASs. So, AASs cause an increase in muscle size as a result of a dose-dependent hypertrophy resulting in an increase of the cross-sectional areas of both type I and type II muscle fibers and myonuclear domains. Moreover, it has been claimed that AASs can increase exercise tolerance by making the muscles more able to overload so protecting them from damage and increasing the level of protein synthesis during recovery [15]. Therefore Nowadays, especially athletes in power sports such as bodybuilding and weightlifting use illegally high doses of AASs to surge their muscle mass and increase their overall performance [49].

The main reasons for administrating AASs are to increase strength and muscle mass. The majority of AAS abusers is non-competitive and appears to be driven mostly by personal goals such as achieving a more ideal body, raising performance levels, or boosting confidence. AASs are typically used in phases referred to as cycles: ‘on cycles’ means specific periods when the users administer AASs and ‘off cycles’ means an AASs -free phase. During ‘on cycles’ users sometimes combine different injectable and oral AASs. This phenomenon is referred to as ‘steroid stacking’ or simply ‘stacking’ . The goal is to gain muscle mass and strength during a cycle while

giving the body time to heal in between cycles. The contents, dose and duration of the cycles are mostly determined by advice from experts. And because muscle mass and strength decrease after cessation of them, multiple cycles or continuous use are believed to be necessary to maintain or further increase gained muscle mass [21, 52].

Anabolic androgenic steroid (AASs) can be administered orally, intramuscularly or subcutaneously as pellet implanted under skin or topically [53].

Stacking" consumption can also include nutritional supplements, complements, or other substances. Alcohol, amphetamines, aspirin, cannabinoids, caffeine, clomiphene citrate, cocaine, codeine, creatine, ephedrine, erythropoietin, furosemide, gamma-hydroxybutyrate (GHB), growth hormone, heroin, insulin, insulin-like growth 1(IGF-1), melanotan, protein powder, tamoxifen, thyroxine, and tobacco are the substances most frequently taken at the same time as anabolic androgenic steroid [53].

Al-Shareef et al. [24] reported that anabolic steroids are completely prohibited in sports, whether in- or out-of-competition. The following organizations prohibit them intake as National Collegiate Athletic Association (NCAA), International Olympic Committee (IOC), U.S. Anti-Doping Agency (USADA), and World Anti-Doping Agency (WAD).

Nandrolone Decanoate(ND);

Nandrolone is also known as 19-nortestosterone and it is an endogenous androgen that exists in male bodies at a ratio of 1:50. It is used medically in the form of esters like nandrolone decanoate (marketed under the name of Deca-Durabolin) and nandrolone phenylpropionate (marketed under name Durabolin) [25]. It belongs to the class II of anabolic androgenic steroids (AASs) [49].

Nandrolone decanoate (ND) is considered to have strong anabolic effects but weak androgenic effects. The reason of its low androgenicity is supposed to be due to the fact that nandrolone is inactivated by 5α-reductase via transformation into the low-affinity androgen receptor (AR) ligand 5α-dihydronandrolone. And this is the reason that nandrolone has a lower incidence and degree of side effects between anabolic androgenic steroids as stated by Tatem et al. [26]. The Androgenic effect of ND stimulates or controls the development and maintenance of male characteristics. This includes the activity of the accessory male sex organs and development of male secondary sexual characteristics [27].

Like testosterone, ND is strongly protein-bound and is found in the blood in both bound and free form. However, It has very low binding affinity for human serum sex hormone-binding globulin (SHBG) [28]. It is administered via intramuscular injection [29]. Nandrolone decanoate's bioavailability varies depending on the place of injection and ranges from 53 to 73% when administered intramuscularly. It was discovered that injections into the gluteal muscle had the maximum bioavailability [28]. It is mainly metabolized by the enzyme 5α-reductase, into 5α-dihydronandrolone, 19-norandrosterone, and 19-noretiocholanolone, which can be detected in urine [30]. ND exhibit a so-called flip-flop pharmacokinetics which means that the ascending portion of the curve represents the deposition of nandrolone and the descending portion of the curve represents the release of ND from the muscle into the general circulation. The recommended therapeutic dose of it for humans is 0.4 mg/kg/day [49].

Tatem et al. [26] mentioned that ND was initially food and drug administration (FDA) approved in 1962 for the treatment of anemia resulting from chronic kidney disease (CKD). While, its use in anemia was largely supplanted in the late 1980s with the introduction of recombinant human erythropoietin (EPO). Patanè et al. [49] also reported that ND is applicable in clinical practice for burns, radiation therapy, surgery, trauma. Moreover, it has also been used for osteoporosis in postmenopausal women, inoperable breast cancer, and for patients on long-term corticosteroid therapy, as well as an adjunct to therapy for conditions characterized by a negative nitrogen balance. The drug is often used off-label to preserve lean mass in human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) associated wasting syndrome. Despite its therapeutic use , it has been abused over the years among athletes ,especially body-builders ,military personnel to improve their performance ,muscular growth and aggressive character [31, 27].

ND injection has been classified as a Schedule III controlled substance under the Anabolic Steroids Control Act of 1990 Due to serious health risks [32].The most common side effects were: endocrine disorders (virilization, gynecomastia, hormonal disorders, cholesterol and lipid disorders, genital and infertility issues); cardiovascular disorders (vascular damage, coagulation disorders, arteriosus hypertension); skin disorders (pricking, acne, skin spots); psychiatric disorders (aggressiveness, mood disorders, sleep disorders, anxiety); musculoskeletal disorders (tendon ruptures); excretory disorders (organ damage); gastrointestinal disorders (organ damage and liver adenomas); neurological disorders (seizures); immune disorders (chronic infection relapse; respiratory disorders (sleep apnea syndrome); genetic disorders (genetic damage) [49].

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