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Review

Andropause: A Neglected Disease Entity

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Abstract

This review aims to bring attention to the growing issue of andropause, a condition that affects men as they age. The literature was identified by searching the major bibliographic databases, including PubMed, Google Scholar, EBSCOhost, Web of Science, and CINAHL. Studies were included if they focused on strategies for reducing and preventing andropause, published between 1980 and 2023. Andropause, which is often overlooked and

misconceived, is the result of a decrease in testosterone production and can result in physical and psychological symptoms such as fatigue, weight gain, decreased libido, and depression. This paper reviews the literature on the prevalence, detection, and management of andropause. It is important for the medical community to recognize andropause, as diagnosing and treating the condition can significantly improve the quality of life. The review canvases several studies to understand andropause comprehensively, highlighting various biomarkers and diagnostic criteria, possible therapies, and potential risks and complications associated with the condition. In addition, this review offers practical suggestions to health professionals, helping them recognize patients at risk of andropause, assess patients for the condition, and provide appropriate treatments. Furthermore, it emphasizes the importance of regular screening and active monitoring for any possible early warning signs of andropause. This review provides a comprehensive overview of andropause, from identification to management. It demonstrates the need for increased awareness and acknowledgment of andropause among medical professionals in order to ensure that all men get the support they need throughout the aging process.

Keywords
Andropause; testosterone; hypogonadism; GnRH; gonadotropin

1. Introduction

Research has shown that testosterone, a hormone vital to male physiology, decreases by 1-2% annually after age 30 [1]. Numerous studies have confirmed that testosterone levels decline with age in men [2-4]. A longitudinal study by Kisighii et al. [5] analyzed data from men aged 29-79 and found that total testosterone levels decreased by 0.2-0.4% annually. Another study by Erenpreiss et al. [6] reported a 1-1.6% decline in testosterone levels per year in men aged 30-40. This decline has also been observed in older men, with a study by Banica et al. [7] reporting a 1.3% decline in testosterone levels per year in men aged 40-70. One study by Liu et al. [8] reported a significant association between low testosterone levels and an increased risk of developing metabolic syndrome, a cluster of conditions that increase the risk of heart disease, stroke, and diabetes. Another study by Laouali et al. [9] found that low testosterone levels were associated with an increased risk of mortality in older men. In addition, testosterone decline has been linked to reduced muscle mass, bone density, and sexual function, leading to decreased quality of life and overall well-being [10]. Moreover, lower testosterone levels have been associated with an increased prevalence of late-onset hypogonadism (LOH) in middle-aged and elderly men, commonly known as andropause. **Andropause,** sometimes referred to as “male menopause,” is a condition that affects males and is associated with a gradual decrease in testosterone levels as men age. This decline in hormones is associated with middle-aged to older men and should not be confused with menopause, which is characterized by a sudden cessation of reproductive hormones [11].

The testosterone concentration initially increases with age until maturity is reached, then declines [12]. This decrease in testosterone levels is accompanied by various physiological changes

commonly related to aging [13]. Research has shown that men may experience a variety of symptoms related to the natural aging process of testosterone production decline [14]. These can include reduced libido, decreased sexual activity, impotence, fertility issues, changes in body composition, reduced body and facial hair, and even osteoporosis.

According to Basaria [15], as men age, their testosterone levels can vary and not remain the same. As we age, it is natural for our hormone levels to changes, which are often associated with various chronic conditions. The term andropause indicates the gradual decrease in testosterone associated with aging. Andropause is sometimes referred to as andropause, which refers to the decrease in the adrenal hormones dehydroepiandrosterone (DHEA) and its sulfate (DHEAS), or somatopause, which refers to the decrease in somatotropic hormones such as Growth Hormone (GH).

The idea of andropause was established a long time ago. However, it has not gained much attention due to numerous conflicting theories questioning its authenticity as a medical issue. Furthermore, men's general reluctance to seek medical care has allowed andropause to stay on the sidelines of the medical profession [16]. Additionally, the ambiguous label "male menopause" has caused recognition issues as well [17].

It has been suggested that men's health may be affected by andropause, a condition related to diminishing testosterone levels. Low testosterone has been linked to an increased risk of cardiovascular disease (2-3×), bone fractures (2×), and other conditions such as metabolic syndrome and type 2 diabetes. Andropause, a reproductive occurrence frequently overlooked, nevertheless exerts notable effects on men, potentially leading to an elevated mortality rate. Additionally, as men age, the body starts making less testosterone, and the levels of another hormone called sex hormone binding globulin (SHBG), which pulls usable testosterone from the blood, begin to increase [18]. This decrease in free testosterone levels due to increased SHBG can contribute to a variety of symptoms, including decreased sex drive, erectile dysfunction, fatigue, and changes in mood and cognition. It can also lead to a decrease in muscle mass and bone density [19]. Hence, monitoring SHBG levels and addressing any imbalances can help manage symptoms of andropause [20]. This review considers the biochemistry, diagnosis, and treatment associated with andropause.

2. Why Andropause

Andropause, also known as male menopause or androgen decline in the aging male (ADAM), is a term used to describe a gradual decline in testosterone levels in men as they age [21]. This decline in testosterone can lead to various physical, psychological, and sexual symptoms that are often associated with menopause in women. However, several other concepts have been proposed to describe this phenomenon, including male climacteric, male climacteric syndrome, penopause, viropause, late-onset hypogonadism (LOH), and PADAM. These terms are often used interchangeably, leading to confusion and a lack of clarity on the subject. Male climacteric refers to when men experience hormonal changes and decreased fertility [22]. It is frequently employed to delineate the male counterpart to menopause in women. Male climacteric syndrome, on the other hand, refers to the symptoms that men experience during this period, such as fatigue, irritability, and decreased libido. Penopause, also known as partial andropause, refers to a stage in a man's life when testosterone levels start to decline. However, a significant amount of

testosterone is still present in the body [21]. This differs from andropause, distinguished by a pronounced and irreversible decline in testosterone levels. Viropause is a concept that suggests that the decline in testosterone levels in men is due to a viral infection, specifically the human immunodeficiency virus (HIV) [23]. Nevertheless, this hypothesis remains unverified, lacking substantiating evidence. Late-onset hypogonadism (LOH) is a term often used to describe the age-related decline in testosterone levels in men [24]. It is associated with symptoms such as erectile dysfunction, decreased libido, and fatigue. LOH is considered a more accurate and scientific terms for andropause, as it takes into account the decline in testosterone levels and the associated symptoms. Androgen decline in the aging male (ADAM) is a term used to describe the gradual decrease in testosterone levels in men as they age [25]. It is often used interchangeably with andropause and LOH. Out of all these concepts, LOH is the most widely accepted and extensively used term to describe the decline in testosterone levels in aging men. It is considered a more accurate and scientific term as it considers the physiological changes and symptoms associated with this phenomenon. Notwithstanding, the term andropause has been chosen over the others because it encompasses the concept of both male climacteric and male climacteric syndrome. It also considers the physical and psychological changes men experience during this stage of life. Moreover, andropause is a more general and inclusive term that can be used to describe the decline in testosterone levels in all men, regardless of the cause. Overall, while there are several concepts and terms used to describe the decline in testosterone levels in aging men, andropause remains the most popular and extensively used term. It encompasses the physiological changes and symptoms associated with this phenomenon and is more general and inclusive.

3. The Endocrine Signal to Maintaining Male Reproductive Health

In males, testosterone is essential in regulating the human sexual response cycle (as demonstrated by [26]). Testosterone influences the diverse phases of the male sexual response cycle, with synthesis occurring in the Leydig cells of the testes and the adrenal cortex. This hormone helps to fuel sexual behavior since it has a direct influence on different steps of the male sexual cycle. Testosterone in men is synthesized in the Leydig cells through a series of five chemical reactions that convert cholesterol into testosterone (refer to Figure 1). This process is regulated by luteinizing hormone (LH) secreted from the pituitary gland. The hypothalamus releases gonadotropin-releasing hormone (GnRH), which triggers the pituitary gland to release LH and follicle-stimulating hormone (FSH), both necessary for male reproductive health.

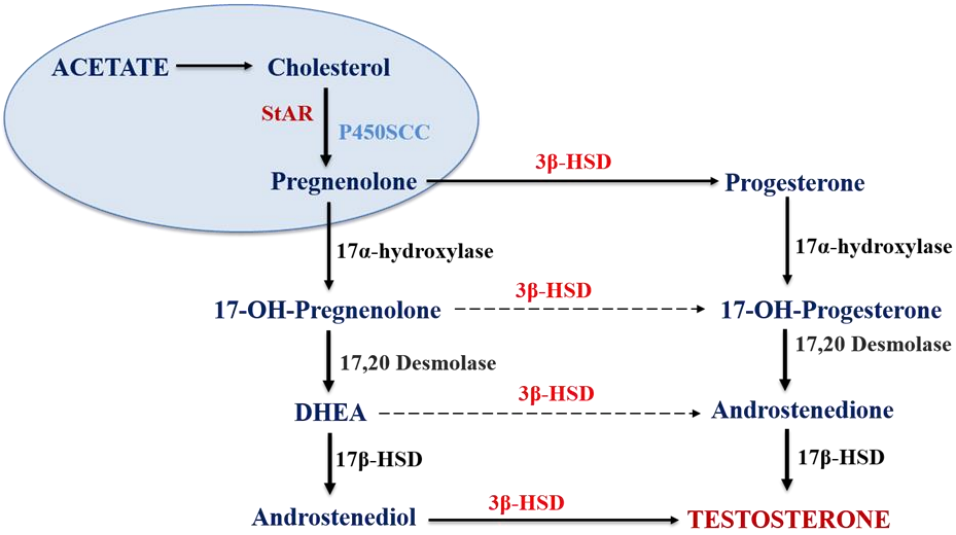

Figure 1 Synthesis of testosterone.

4. Testosterone Secretion

Testosterone production in men relies on a steady supply of cholesterol to the Leydig cells. Cholesterol can be either synthesized de novo, liberated from reserves of cholesterol esters within lipids, or obtained from lipoproteins circulating in the bloodstream [27]. Studies have shown that cholesterol for steroidogenesis in mice and rats is mostly synthesized from scratch [28].

The first step towards creating steroids (steroidogenesis) involves converting cholesterol to pregnenolone. This conversion occurs in the mitochondria of cells in the adrenal glands and gonads. It is catalyzed by the enzyme cholesterol side-chain cleavage enzyme (CYP11A1). Once LH binds to the receptors on the Leydig cell, cAMP stimulation results in the rapid synthesis of the transport molecule. This molecule transports cholesterol across the inner membrane of the mitochondria, which triggers the conversion of cholesterol into Pregnenolone - a rate-limited process [29]. Pregnenolone is first moved from the mitochondria to the smooth endoplasmic reticulum. From here, a sequence of enzymatic reactions happens to create testosterone.

The phosphorylation of steroidogenic acute regulatory (StAR) protein, which is responsible for transferring cholesterol to the inner mitochondrial membrane that is then converted to pregnenolone through CYP11A1 (P450scc) [27], increases. Subsequently, pregnenolone passively diffuses out of the mitochondria and undergoes further androgen biosynthesis in the cell's smooth endoplasmic reticulum [30]. Testosterone can interact directly with target cells or be transformed into its main metabolite - dihydrotestosterone (DHT) - by binding to the androgen receptor. Research has indicated, however, that DHT has a higher affinity to the androgen receptor than testosterone.

5. Testosterone Functions and Progression

Testosterone is vital to the health and well-being of men. It supports the development of male characteristics, sexual behavior and performance, and sperm production. It also helps manage muscle mass, fat distribution, bone strength, red blood cell count, facial and body hair, and libido [31, 32]. Evidence supports that males attain normal plasma testosterone levels (10-35 nmol/L) by their late teens, approximately 17 years old. While male testosterone remains stable until 30-40

years, research has shown that it decreases gradually over time, with the rate of decline estimated at 1.2% each year [33]. Studies also suggest that testosterone in males aged 70 years old is lower in comparison to younger males, as much as 35% lower [14]. There is a newer population of males aged 65 and above who have andropause, a form of hypogonadism, as a result [34].

6. Pathophysiology of Andropause

Testosterone production is regulated by the Leydig cells in the interstitial compartment between the seminiferous tubules, stimulated by luteinizing hormones from the anterior pituitary gland. This hormone is essential for the development and proper functioning of the male reproductive system from conception to adulthood. During pregnancy, testosterone production is increased by the emergence of Leydig cells from their mesenchymal precursors [33]. At birth, testosterone levels are high due to fetal Leydig cells; however, these levels gradually decline with age as the cells are lost. From age 30 onwards, testosterone levels drop at a rate of 0.4-2% per year [33]. This continuous decrease can lead to hypogonadism, a condition characterized by abnormally low levels of serum testosterone at more advanced ages.

Hypogonadism is a condition that can be divided into two distinct categories: primary and secondary. If a decrease in luteinizing hormone levels does not accompany the decline in testosterone, hypogonadism is classified as primary. However, if the decrease in testosterone is due to a reduction in luteinizing hormone levels, it is classified as secondary hypogonadism [35]. In some cases, both primary and secondary hypogonadism may be present [36, 37]. Late-onset hypogonadism (LOH) is the basis of "Andropause," and it is associated with a decrease in testosterone levels with the onset of age. LOH is categorized as a combined primary and secondary hypogonadism due to impairment in the endocrine function of both the testes and the pituitary [38]. The symptoms of LOH include loss of libido, erectile dysfunction, loss of muscle mass, increased body fat, anemia, osteoporosis, depressed mood, decreased vitality, sweating, and hot flushes. Additionally, LOH also increases the chances of developing metabolic syndrome and cardiovascular disease [38].

7. Leydig Cells Depletion and Andropause

As people age, the process of homeostasis - the hypothalamic-pituitary-testicular axis - is affected. This results in a gradual decrease in the sensitivity of the hypothalamus to testosterone. The concurrent reduction in the Leydig cell's response to LH can be attributed to the long-term overstimulation of LH and FSH. This produces desensitization of the sex hormone receptors, producing less testosterone. It has been noted in humans that as testicular aging occurs, changes in the morphology of the parenchyma can be seen [39]. These changes include the presence of sclerosed tubules and tubules with various morphological abnormalities in the germ cells. Additionally, a decrease in the number of Leydig cells has been observed in older individuals.

In males under 25, there are about 432 million Leydig cells [40]. However, beyond the age of 40, the number of Leydig cells tends to decrease to 44% [40]. Even though the morphology of Leydig cells does not seem to change much over time, there is evidence that the cells may undergo de-differentiation and involution when cytoplasmic or intranuclear inclusions are acquired [41, 42]. Matzkin et al. [43] proposed that shrinkage of the testicles is believed to result from a diminished blood supply caused by atherosclerosis of the arteries in the area. Subsequent animal studies on

aging rats further illustrated the reduction in Leydig cell volume with age [44, 45]. The suggestion has been made that the decrease in Leydig cells could be the origin of the Andropause phenomenon in men. However, research by Papadopoulos and Zirkin [42] has found that Leydig cells in elderly males (aged over 65) are less sensitive to LH stimulation than those in younger men. Studies using Brown Norway rats as an animal model of aging have shown that, even though the number of Leydig cells per testis is consistent in both the young and old rats, there is a decrease in testosterone levels in the older animals. The suggestion has been put forth that there exists a disruption of the HPT axis in aging males, which has been attributed to a combination of changes in testicular and germinal tissue structure and alterations in HPT axis hormone levels [46].

As men age, the Leydig cells found in the testicles become prone to defects, such as changes in Steroidogenic InteracTomE (SITE), increased cell oxidation, and reduced androgen formation. This endocrine dysfunction is proven by the decreased amount of non-steroidogenic hormone-insulin-like peptide 3 (INSL3) secreted by Leydig cells of older men compared to the amount secreted by younger men [47].

Rubens et al. [48] conducted experiments demonstrating that Leydig cells exhibited diminished responsiveness in older males compared to younger ones. When human chorionic gonadotropin (HCG) was used to stimulate males over 65, the mean testosterone production was 142% higher in younger men yet only 85% higher in older men [41, 48]. Studies conducted in vitro using the Brown Norway rat model of male reproductive aging have supported the relationship between age-related decline in Leydig cell responsiveness to LH and testicle shrinkage. For example, when isolated Leydig cells from young and old rats were stimulated with LH, there was a reduced basal and diminished LH-stimulated testosterone concentration in older mice in comparison to younger ones [49].

Studies such as Paniagua et al. [39] and Petersen et al. [50] have shown that advancing age does not necessarily lead to a decrease in the number of Leydig cells, even though it could lead to a reduction in the production of both testosterone and INSL3. Research has found that aging Leydig cells can suffer from impairments in their function, which can be evidenced by decreased cAMP productions stimulated by LH [51], reduced expression and activity of steroidogenic enzymes [52], and less expression of STAR with Translocator protein (TSPO) located in the outer mitochondrial membrane [53]. All these deficits can result in testicle shrinkage caused by arterial hardening due to atherosclerosis. Studies conducted in laboratory environments suggested that as individuals age, the number of Leydig cells decreases in parallel with decreased INSL3 expression; however, this did not appear to affect the capacity of the testis to produce steroids in vitro [41].

8. Gonadotropin-releasing Hormone and Andropause

Gonadotropin-releasing hormone (GnRH), secreted by the hypothalamus, governs the intensity and frequency of LH and FSH hormone release from the anterior pituitary. It does this in a pulse-like manner. Recent studies have suggested that as men age, there is a decrease in the secretion of GnRH from the hypothalamus due to alterations in the pulse amplitude, thereby influencing the frequency of gonadotropin release [54, 55]. This decline in GnRH outflow is also believed to not lead to testicular shrinkage in healthy men [54]. However, it is possible that arterial hardening caused by atherosclerosis could increase the sensitivity to negative feedback or lead to intrinsic

production defects, which could, in turn, lead to testicular shrinkage in some men. This is reported in animal models [56].

The decrease in the levels of gonadotropins and the expression of GnRH genes in the medial preoptic area of male rats as they age is thought to be a consequence of testicular feedback [56-58].

Leydig cells from both aged and young rats have noticed a decrease in binding sites of LH [59, 60]. Despite this, when stimulated with LH, the young rats showed high cyclic adenosine monophosphate (cAMP) production, yet the old cells produced far less cAMP [61]. This observation may point to defects in LH-cAMP signaling that limit the responsiveness of old Leydig cells to LH stimulation. Reduced cAMP levels brought about by arterial hardening may lead to decreased expression of StAR and other steroidogenic enzymes associated with testosterone production [52, 62]. Ultimately, this could lead to testicular shrinkage.

Although the number of binding sites on Leydig cells and the affinity of the available sites for LH undergo alteration due to aging, the decreased capacity of old Leydig cells to yield cAMP is not attributed to a deficiency in LH binding. Interestingly, the number of binding sites and binding affinity both underwent greater cell changes in younger rats. However, the Leydig cells of aged rats remained unchanged in their response to LH.

Studies have suggested that Leydig cells in the testicles contain a small number of LH receptors, and the production of maximal cAMP (cyclic adenosine monophosphate) can be stimulated by hormone binding to these receptors, as reported in a paper by Browne and Bhalla [63].

9. Oxidative Stress and Andropause

As Leydig cells age, the intracellular environment becomes more oxydative. This environment is caused mainly by reactive oxygen species (ROS) produced by the P450 in the mitochondria and smooth endoplasmic reticulum [64]. Additionally, ROS is generated through the mitochondrial electron transport system [65].

Therefore, the increased oxidative environment brought on by aging in Leydig cells may result in testicular shrinkage due to arterial hardening caused by atherosclerosis. Atherosclerosis, characterized by the accumulation of fatty deposits leading to arterial hardening and narrowing, can diminish blood flow to the testes. Consequently, Leydig cells may receive inadequate oxygen and nutrient supply. As a result, Leydig cells become more susceptible to oxidative stress and damage. The increased oxidative environment in Leydig cells can lead to testicular shrinkage in two ways. Firstly, oxidative stress can directly damage Leydig cells, leading to cell death and decreased testosterone production. Testosterone is essential for maintaining the size and function of the testes, and a decrease in its production can result in testicular shrinkage. Secondly, the decreased blood flow to the testes caused by atherosclerosis can also contribute to testicular shrinkage. Reduced blood flow means Leydig cells do not receive enough oxygen and nutrients, leading to their dysfunction and eventual death. Consequently, this may result in decreased testosterone production and testicular shrinkage.

As people age, steroidogenesis is impacted due to interference with the intracellular redox balance. As a result, there is an increased production of ROS, which has a significant influence on the formation of cyclic adenosine monophosphate (cAMP) from the adenosine triphosphate (ATP) (as illustrated in Figure 2). This disruption in cholesterol transport to the mitochondria further

impacts the formation of steroid hormones (as suggested by a study conducted by [59]). The increased ROS in the Leydig cell also leads to increased Cyclooxygenase (Cox2) production and redox-sensitive mitogen-activated protein kinase (MAPK) synthesis. Studies have shown that ROS produced by normal cell metabolism can harm DNA, proteins, and lipids [66]. It has been established that this damage caused by free radicals can contribute to cellular aging [67-70]. Oxidative damage may lead to a decrease in LH's ability to induce cAMP production and disruption of membrane fluidity, which could impair the LH-cAMP cascade [71-75]. Therefore, this may ultimately result in testicle shrinkage due to arterial hardening caused by atherosclerosis.

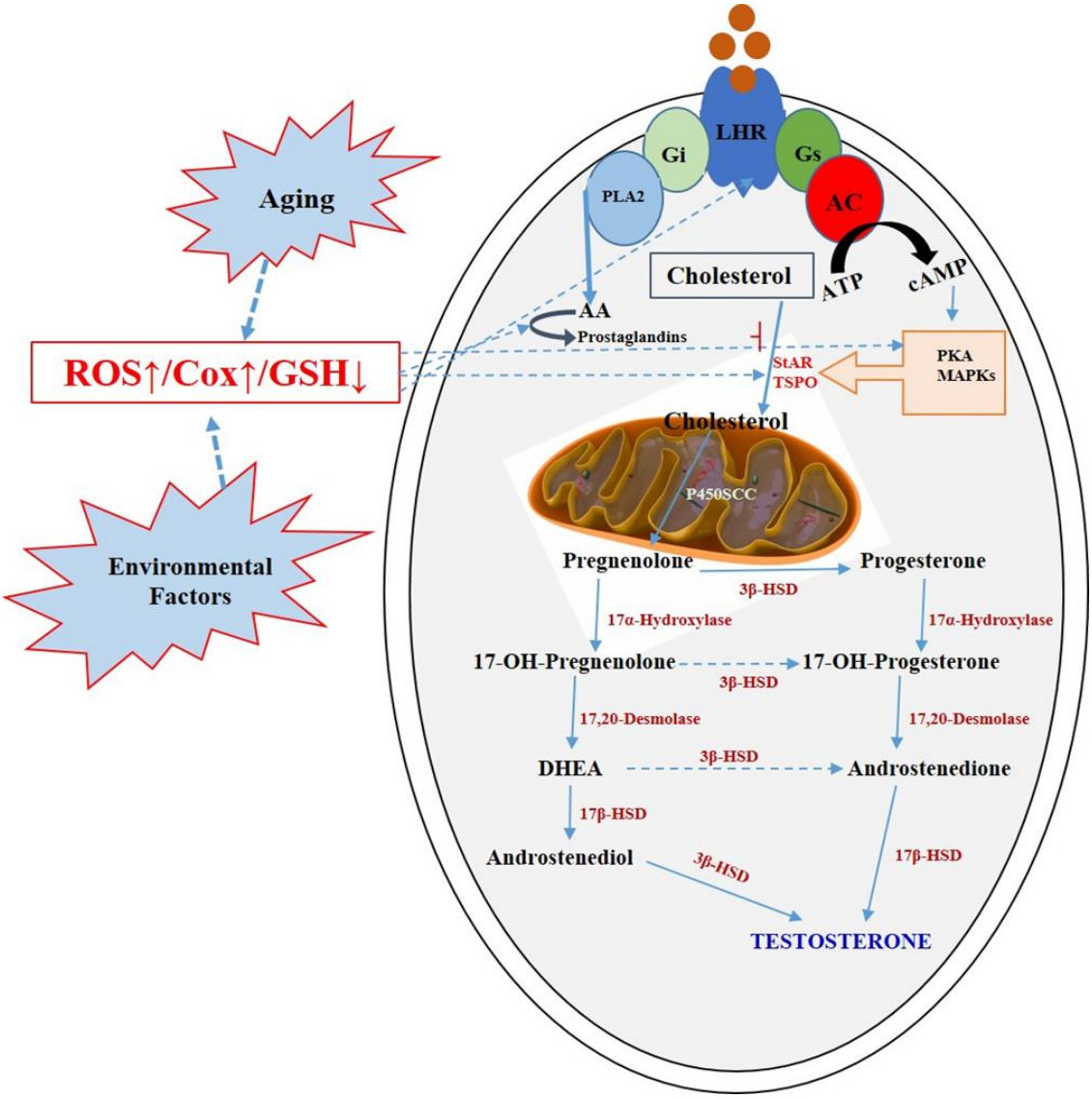

Figure 2 Pathophysiology of Andropause (The role of Ageing and Environmental factors on Leydig cell Physiology).

10. Effects of Andropause

Studies have revealed that andropause can lead to several negative consequences, including an increase in body fat, a loss of libido, difficulty achieving erections, muscle loss, a depressed mood,

weak bones, and a general lack of energy. These changes have a negative impact on the quality of life of older men.

11. Andropause and Cardiovascular System

Testosterone levels, the primary male hormone, reduce as men reach the age of forty and beyond. Coinciding with the reduction in testosterone is a concomitant increase in the risk of cardiac problems and mortality [76-79]. Therefore, men aged forty and over are more likely to experience cardiovascular issues as well as an overall decrease in testosterone levels. A significant prevalence of testosterone deficiency was found among men with congestive heart failure (CHF), according to a clinical study [80]. Moreover, a population-based prospective study unveiled an association between testosterone and the incidence of ischemic heart disease, which could be ascribed to insulin resistance syndrome [81]. Research by Kaur and Werstuck [82] suggests that testosterone can have multiple effects on aging men and men with low testosterone levels. Specifically, they suggested it can shorten the heart-rate-corrected QT interval, improve glycemic control, induce vasodilation, be prothrombotic, and have anti-obesity effects. Furthermore, they noted that men with low testosterone levels tend to accumulate more visceral fat, likely due to the effects of andropause. The buildup of arterial hardening can significantly contribute to insulin resistance and an atherogenic lipid profile. Furthermore, testosterone has been recognized to enhance spatial cognitive capacities, promote positive mood changes, and mitigate the risk of testicular shrinkage induced by atherosclerosis.

12. Andropause and Body Mass Index

Testosterone, the main male androgen hormone, has been found to carry out a variety of anabolic and catabolic effects. As an anabolic hormone, it can help decrease visceral fat buildup by increasing androgen receptors. This activation initiates a lipolytic process, increasing lean body mass through the activation of Wnt signaling. This process encourages the differentiation of mesenchymal cells into muscle fibers [83]. Maneschi et al. [84] indicated that testosterone hinders the transformation of mesenchymal cells to fat cells, which is regulated by PPARγ and CEBPα, through suppressing them. It has been observed that lower testosterone levels in men correspond to increased lean muscle wastage and a shift in the fat storage pattern from subcutaneous (under the skin) to visceral (in the abdomen) fat [85]. This phenomenon is especially pronounced in individuals who have a diagnosis of obesity.

13. Andropause Muscle Mass and Bone Density

Testosterone is a hormone that influences muscle mass by activating androgen receptors, activating pathways associated with protein synthesis. Muscle mass is crucial in determining strength and power; the more muscle mass a person has, the greater their capacity to generate force. Therefore, a decrease in testosterone caused by shrinkage in testicles due to arterial hardening caused by atherosclerosis would decrease an individual's muscle mass, strength, and power [86]. This decrease can have serious repercussions, such as reducing skeletal muscle size and strength [87]. Multiple mechanisms, including the influence of testosterone on the commitment of pluripotent mesenchymal cells, can cause such changes in skeletal muscle mass.

As a result, shrinkage of the testicles due to decreased testosterone may be associated with arterial hardening caused by atherosclerosis [88]. When testosterone production decreases, it can impede the growth of muscle mass.

Andropause, otherwise known as male menopause, has been linked to various health concerns, such as a drop in testosterone levels. This decline in testosterone can lead to a decrease in muscle mass, bone density, and an increase in visceral fat, as well as a reduction in muscle strength and power, functional capacity, sexual function and libido, mood changes, and cognitive function [21, 89].

14. Andropause: Diagnostic Criteria and Biomarkers

Hormonal biomarkers are the most reliable and often the most direct way to detect andropause. Common hormones tested for include testosterone, FSH, and LH. Testosterone levels are considered to be the primary biomarker when diagnosing andropause, with levels typically lower than those typically seen in a healthy 30-year-old male. Sex hormone-binding globulin (SHBG), estradiol, dehydroepiandrosterone sulfate (DHEAS), thyroxine, melatonin, and prolactin [90] can help confirm the presence of andropause by measuring their lower-than-normal ratio when testosterone levels are low. A low testosterone level, along with elevated FSH and LH levels, can confirm the diagnosis. DHEA is a precursor to testosterone, and its levels also decrease with age. SHBG is a protein that binds to sex hormones; its levels may increase with age.

Estradiol is a hormone produced primarily in the ovaries of women and in the testes of men. It regulates the reproductive system and plays a crucial role in bone health, mood, cognition, and cardiovascular health. In men, estradiol is produced by converting testosterone by an enzyme called aromatase. As men age, their testosterone levels decrease, which can also lead to a decrease in estradiol levels. One of the most significant biomarkers of andropause is the ratio of testosterone to estradiol. A study identified a correlation between lower testosterone-to-estradiol ratios in men and an increased likelihood of experiencing symptoms of andropause [91]. This observation implies a potential involvement of estradiol in the onset of andropause and suggests its potential utility as a biomarker for this condition. Furthermore, research has shown that estradiol levels may also be associated with specific symptoms of andropause. For example, a study found that lower estradiol levels were associated with increased sexual dysfunction in aging men [92]. Another study found that higher estradiol levels were associated with better cognitive function in older men [93]. In addition to being a potential biomarker for andropause, estradiol may also be a target for treatment. Testosterone replacement therapy has been the primary treatment for andropause, but it can also lead to an increase in estradiol levels. This has led to the development of new treatments that specifically target the conversion of testosterone to estradiol, known as selective estrogen receptor modulators (SERMs). While much remains to be elucidated regarding the role of estradiol in andropause, current research indicates that it may serve as a significant biomarker for the condition and could be a focal point for treatment. However, further research is needed to fully understand the role of estradiol in andropause and its potential as a biomarker and treatment target.

Thyroxine is a hormone produced by the thyroid gland that plays a crucial role in regulating metabolism. As men age and testosterone levels decline, there is often a corresponding decrease in thyroxine levels. A low level of thyroxine is associated with increased severity of andropause

symptoms, including sexual dysfunction, decreased muscle strength, and depression [94]. This highlights the importance of using thyroxine as a biomarker for andropause, as it can provide valuable information about the severity of symptoms and guide treatment decisions.

Melatonin is a hormone produced by the pineal gland in the brain and is responsible for regulating the body's sleep-wake cycle. It is also known as the 'darkness hormone' as its production is stimulated by darkness and inhibited by light. While melatonin is commonly associated with sleep, it has other important bodily functions, including its role as an antioxidant and anti-inflammatory agent. Recent studies have shown that melatonin levels decrease with age, and this decline is more pronounced in men compared to women [95]. This decrease in melatonin has been linked to the development of andropause symptoms. Studies have found that men with lower levels of melatonin are more likely to experience symptoms such as low libido and erectile dysfunction [96]. One study conducted by researchers at the University of Granada in Spain found that men with andropause had significantly lower levels of melatonin compared to healthy men of the same age [97]. They also found that these men had a higher risk of developing cardiovascular disease, which is a common complication of andropause. Another study conducted in Italy showed that men with lower levels of melatonin had a higher risk of developing metabolic syndrome, a cluster of conditions including high blood pressure, high blood sugar, and excess body fat around the waist [98]. This is significant as metabolic syndrome is also associated with an increased risk of cardiovascular disease and type 2 diabetes, both of which are common in men with andropause. Melatonin has also been found to have an impact on other biomarkers of andropause, such as testosterone levels. One study found that melatonin supplementation in men with low testosterone levels led to an increase in testosterone levels and improved symptoms of andropause [89]. Based on these findings, melatonin levels may be a biomarker for andropause and related health complications. Measuring melatonin levels in aging men could help identify those at risk for developing andropause and its associated conditions. It could also be used to monitor the effectiveness of treatment options, such as melatonin supplementation, in managing andropause symptoms.

Prolactin is a hormone primarily known for its role in lactation and breast development in women. However, it also plays a significant role in men's health. Prolactin levels increase with age in men, and studies have shown that elevated levels of prolactin are associated with a variety of symptoms commonly seen in andropause [11], such as decreased libido and erectile dysfunction. One study published found that men with elevated prolactin levels had significantly lower testosterone levels and were more likely to report symptoms of andropause [11]. This suggests that measuring prolactin levels could be a useful biomarker for identifying men who may be experiencing andropause. Additionally, research has shown that prolactin levels can be affected by lifestyle factors such as stress and sleep patterns. Chronic stress can increase prolactin levels, which may contribute to the symptoms of andropause. Similarly, disrupted sleep patterns, which are common in men experiencing andropause, have been linked to increased prolactin levels. This highlights the potential for using prolactin as a biomarker for diagnosing andropause and monitoring the effectiveness of lifestyle interventions in managing this condition. Furthermore, prolactin may also have a role in the development of other conditions commonly associated with andropause, such as cardiovascular disease and metabolic syndrome. A study also found that men with elevated prolactin levels were at a higher risk for developing these conditions [99]. This suggests that measuring prolactin levels could also be beneficial in identifying men who may be at

risk for these conditions. While testosterone remains the most widely accepted biomarker for andropause, the growing body of research on prolactin suggests that it could also be a valuable biomarker for this condition. Measuring prolactin levels in men who are experiencing symptoms of andropause could help healthcare providers make a more accurate diagnosis and develop a more comprehensive treatment plan.

Some studies suggest that testosterone levels in men can begin to decrease as soon as the age of 30 [100]. However, other factors, such as lifestyle habits and disease states, may also impact testosterone levels. Therefore, serum testosterone levels must be assessed with other signs and symptoms to determine if andropause is present. In addition to testosterone levels, other biomarkers and diagnostic criteria are often used in the diagnosis of andropause. These include changes in body composition, lipid profile, and hemoglobin/hematocrit levels [101]. Psychological symptoms, such as decreased libido and depression, are also commonly seen in men with andropause. Furthermore, erectile dysfunction has been identified as an important criterion for diagnosing andropause [100, 102].

The Androgen Deficiency in the Aging Male (ADAM) questionnaire is one such criterion, which consists of 10 questions related to symptoms of andropause [103]. A score of 20 or more is considered to suggest andropause, and any score below this is likely to exclude andropause [103]. Other criteria proposed include the Aging Male Symptoms (AMS) scale and the Aging Males' Rating Scale (AMRS). However, the ADAM questionnaire is the most reliable criterion for diagnosing andropause.

15. Diagnostic Standard for Andropause

Serum testosterone levels vary due to daily and yearly cycles, secretion patterns, and measurement differences. A blood sample should be taken between 7 AM and 11 AM to assess testosterone. Testosterone is mostly bound to proteins, with only a small portion being 'free' and available. SHBG levels can affect total testosterone, so it is crucial to confirm low levels and consider free or bioavailable testosterone in some instances. Clinicians should use the reference range for young, healthy men to assess whether symptoms are linked to low testosterone levels [11]. According to Nandy et al. [104], the standard diagnostic measuring value can be categorized as: normal value (greater than 400 ng/dl), borderline value (200-400 ng/dl) and low value (less than 200 ng/dl) (Figure 3). However, the typical threshold for testosterone in young men is approximately 300 ng/dl (10.4 nmol/l), with symptoms being more prevalent below this level. Professional organizations agree that replacement therapy is not necessary for total testosterone levels above 350 ng/dl (12 nmol/l), and treatment is beneficial for patients with levels below 230 ng/dl (8 nmol/l) [11]. Current methods for measuring testosterone can differentiate between hypogonadism and normal levels in adult men. While equilibrium dialysis and sulfate precipitation are considered the gold standard, calculated values are preferred. The threshold values for bioavailable testosterone vary depending on the method used, and while salivary testosterone is a reliable alternative, it is not recommended for general use [11]. To differentiate between primary and secondary hypogonadism, measuring LH and FSH serum levels is necessary. Elevated levels indicate primary hypogonadism, while low levels are indicative of secondary hypogonadism. In cases where testosterone levels are low but LH and FSH are normal, this may suggest defects in

the hypothalamus or pituitary gland. If the testosterone concentration is below 150 ng/dl, it is recommended to conduct pituitary imaging and measure prolactin levels [11].

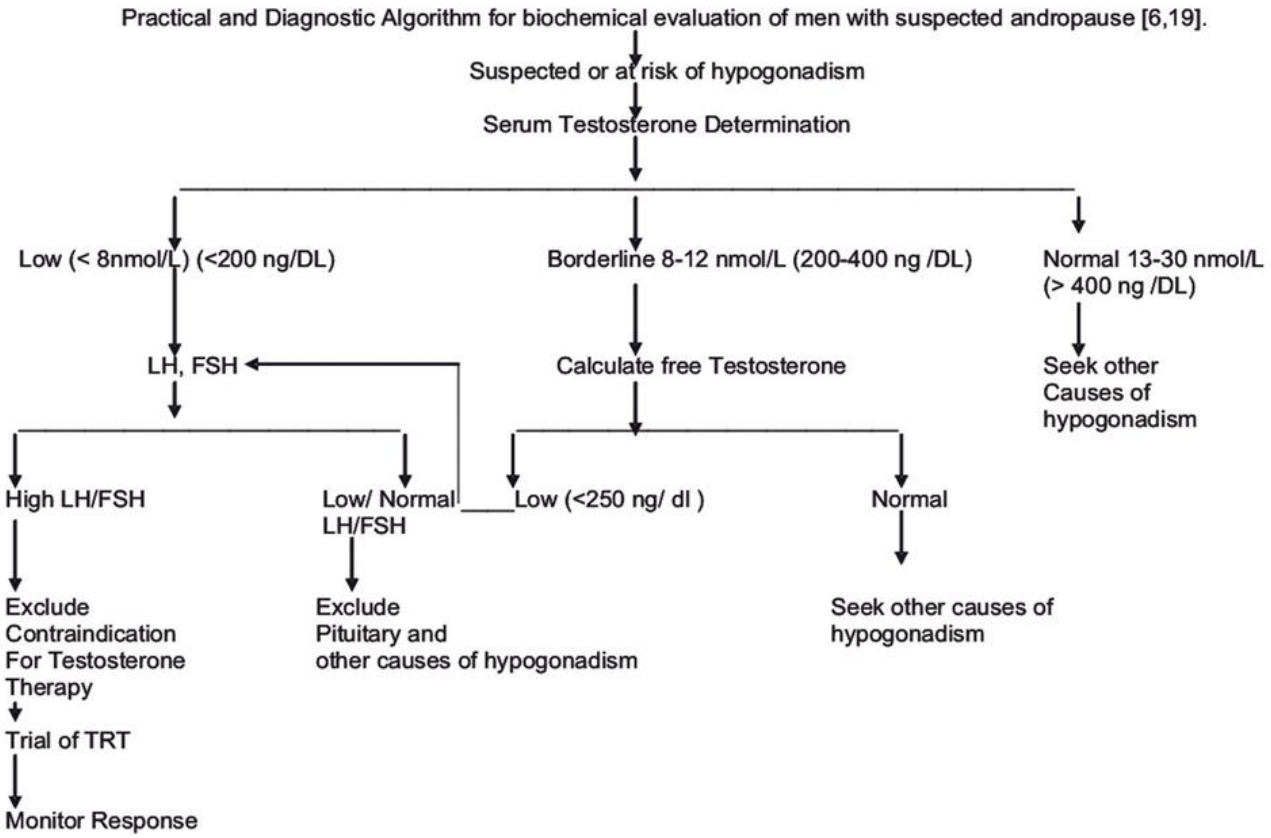

Figure 3 A diagram showing diagnosis and treatment for Andropause (Adapted from [104].

16. Possible Therapies of Andropause

Given the importance of testosterone for male physical and mental health, many treatments for andropause have been developed. One of the primary treatments is hormone replacement therapy (HRT), which is the administration of testosterone to replace the decline in the hormone's production. Studies have found TRT to be effective in alleviating the symptoms of andropause, including fatigue, muscle loss, and loss of libido. In addition, it may be beneficial for improving mental health, with evidence suggesting that it reduces depression risk [105] and is associated with improved quality of life [106, 107]. Overall, the most relevant outcomes of androgen deficiency and clinical symptoms of hypogonadism who receive testosterone replacement therapy are overall survival, symptoms, morbid events, functional outcomes, and quality of life [108-111]. For men with low testosterone levels and sexual dysfunction, the evidence has been reasonably consistent in demonstrating a beneficial effect on increased libido [111]. Other sexual function symptoms (e.g., erectile dysfunction) are also likely to be improved, but the evidence is less strong. For other symptoms, there is evidence that lean body mass increases, body fat decreases, and bone mineral density increases with testosterone therapy [109, 110]. However, the impact of these changes on functional status and fractures is less clear. For outcomes such as decreased energy, depression, quality of life, and cognition, the evidence is limited and inconsistent in

reporting the benefits of replacement therapy [109, 110]. The evidence is sufficient to determine that the technology significantly improves the net health outcome.

Another potential therapeutic approach involves lifestyle modification. This encompasses dietary adjustments, exercise regimens, and stress management techniques to alleviate some of the symptoms associated with andropause. Lifestyle modifications can help improve mood, energy, and sexual functioning, as well as provide a better sense of well-being in those suffering from the effects of andropause [112, 113].

A further potential therapy is herbal remedies. Certain herbs are beneficial in improving the symptoms of andropause. These include saw palmetto, which can help improve sexual functioning and reduce fatigue [114], and ashwagandha, which can help boost energy and reduce stress levels [115].

17. Public Awareness on Andropause

With the rising numbers of older men, andropause is poised to emerge as a significant healthcare problem concern necessitating attention to avert disability and illness. According to Comhaire [116], the published literature on andropause, hence the poor public knowledge about its diagnosis and treatment. Furthermore, the findings from researchers, including primary care physicians, showed limited awareness and understanding of andropause [117]. Research conducted to evaluate how socio-demographic variables affect the knowledge and opinion of people on andropause among healthcare practitioners in Ile-Ife, Nigeria, showed that 23% of the participants considered andropause a positive male phenomenon [118]. In another study by Abootalebi et al. [119], about 48.8% of subjects are familiar with andropause. Their primary information sources included colleagues and friends (13.4%), continuous medical education (10.7%), health media advertisements (9.5%), printed publications (9.2%), and significant medical conferences (6.2%) [119].

Altogether, public awareness about andropause among males and healthcare practitioners is poor. GPs (General practitioners) are the first-line healthcare providers and function as family physicians, maintaining frequent contact with patients [120]. However, Pommerville *et al.* [121] opined that the knowledge of andropause among primary care physicians is adequate, though noticeable deficiencies existed regarding the depth of understanding and expertise regarding the management and treatment of this condition. Regrettably, they may lack the necessary academic preparedness to make informed decisions. Therefore, there is a compelling need for educational interventions and courses tailored to this end.

The initial stage of effective health education on andropause would involve assessing the subjects' knowledge and disposition, guiding the subsequent stages to improve the men's well-being, and decreasing vulnerability to andropause [122].

A significant challenge that public health education should target is the fact that men resist the idea of male menopause. A substantial number of men unknowingly reject the existence of these alterations, particularly those related to sexuality, and hold an unfavorable stance toward andropause. Historically, the medical community's perspective on andropause was linked with pessimism [121]. Nevertheless, physicians' understanding expands as science progresses, and many inquiries are conducted in this domain. With heightened knowledge and increased public awareness, one can anticipate the emergence of more favorable attitudes. The optimism of

physicians holds significant importance since it bolsters their stance and enhances their competence by ameliorating practice quality, diagnostic capabilities, and treatment modalities. This, in turn, decreases andropause-related complications, influences the attitude of the general male population, and helps cultivate positive perspectives. Furthermore, it contributes to enhanced public enlightenment because greater exposure and discourse about andropause facilitate its acceptance [104].

18. Conclusions

Since aging is inevitable in males, testosterone plays a pivotal role in the integrity and maintenance of systems and organs. However, the decline in testosterone concentration is the hallmark of failing health challenges and quality of life in males. Although the use of testosterone replacement therapy to normalize testosterone levels, the effect of the therapy is poorly established due to the poor actions of the androgen receptors. Hence, future studies should examine the androgen receptors to be able to provide several important benefits associated with testosterone in terms of sexual life, mental activity, metabolism, and bone/musculature integrity.

Author Contributions

Conceptualization: A.F.A., O.T.D., O.M.O., A.A.A., Data maintenance, creation of the original draft: A.L.O., O.M.O., A.F.A. Review and contributions: Conceptualization, A.G.B., O.M.O., O.P., Data maintenance, creation of the original draft: D.S.N., O.M.O., A.F.A., Supervision: A.F.A., O.M.O., Validation: A.A.M., O.M.O.; Funding acquisition: A.F.A., O.M.O. All authors have read the manuscript and consented to publication.

Competing Interests

The authors have declared that no competing interests exist.

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