Received: 17 October 2024 | Accepted: 26 December 2024

DOI: 10.1002/uro2.115

UroPrecision Open Access

REVIEW ARTICLE

Testosterone and men's health: An in-depth exploration of their relationship

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Abstract

Testosterone plays a pivotal role in male health throughout the lifespan. Men generally exhibit higher serum testosterone levels than women, influencing critical aspects of male physiology. It drives normal sexual differentiation during fetal development, promotes the acquisition of pubertal traits, and induces the development of secondary male sex characteristics. While testosterone levels naturally decline with age, this decrease varies greatly between individuals, indicating that aging alone does not account for any specific testosterone level. The interindividual variability highlights the influence of both genetic and environmental factors on testosterone production. Abnormal changes in testosterone levels, whether excessive or deficient, can have significant implications for men's health, contributing to conditions such as hypogonadism, cardiovascular disease, sexual disorders, and metabolic disorders. Precision medicine provides personalized testosterone treatment options for hypogonadism, taking into account genetic, hormonal, and lifestyle aspects to improve outcomes. This tailored approach is also relevant in dealing with broader reproductive and sexual health issues, ensuring effective and individualized care. This review focuses on testosterone's varied involvement in men's health, using biomarkers and precision medicine breakthroughs to inform tailored therapy and future research.

KEYWORDS

aging, androgen receptor, cardiovascular disease, hypogonadism, men's health, metabolic disorders, testosterone

1 | INTRODUCTION

Testosterone, a steroid hormone, is primarily produced by the testes in males, with smaller amounts generated by the adrenal glands in both sexes and the ovaries in females. It functions as an anabolic steroid and is the main hormone involved in male sex characteristics. Testosterone plays a critical role in the development of male reproductive tissues such as the testes and prostate, while also promoting secondary sexual characteristics like increased muscle and bone mass and body hair growth. Balanced levels of testosterone are essential for overall health and have been linked to the prevention of certain diseases[1].

Testosterone is vital for men's physical and emotional health, extending beyond reproductive functions. It supports the growth and maintenance of muscle mass and strength, enhancing protein production required for

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muscle growth and repair. Testosterone also helps preserve bone density, as low levels can lead to reduced bone mass, increasing the risk of osteoporosis and fractures[2].

Additionally, testosterone influences fat distribution in the body, with low levels often linked to increased abdominal fat. It also stimulates red blood cell production, boosting stamina and energy. Adequate testosterone levels are associated with improved mood, cognitive function, and a reduced risk of depression. On the other hand, low testosterone can contribute to erectile dysfunction and decreased sexual desire. Furthermore, testosterone is crucial for metabolic processes and cardiovascular health, where appropriate levels can help regulate cholesterol and reduce the risk of heart disease[3].

A blood test is the most common method to measure testosterone, assessing both free testosterone and testosterone bound to proteins such as albumin and sex hormone-binding globulin (SHBG). The bioavailable testosterone test measures free testosterone and the fraction loosely bound to albumin, while the free testosterone test offers a more precise assessment of the unbound hormone. Blood samples are typically collected in the morning when testosterone levels peak due to circadian rhythms[3]. Additional tests, such as SHBG and luteinizing hormone (LH) assays, may be performed to assess the hypothalamic-pituitary-gonadal (HPG) axis. For adult males, total testosterone levels should range from 300 ng/dL to 1000 ng/dL or 10 nmol/L to 35 nmol/L, with free testosterone levels between 5 and 20 pg/mL[3,4]. About 30% of men aged 40–79 experience testosterone deficiency (TD), a condition that becomes more common with age and health issues such as obesity, diabetes, and hypertension.

Older men often experience significantly lower testosterone levels, which can lead to symptoms such as decreased strength, muscle mass, bone density, increased body fat, reduced libido, erectile dysfunction, and mood changes like irritability and depression. While the normal testosterone range may vary slightly in older men, levels below 300 ng/dL are generally considered low and may warrant further testing or treatment[5].

Testosterone is a key player in reproductive and sexual medicine, influencing both the anatomical and functional aspects of male reproductive health. In the testes, testosterone promotes sperm production by acting on Sertoli cells, which is essential for male fertility. Furthermore, testosterone keeps accessory reproductive organs like the prostate and seminal vesicles functioning, which help to produce seminal fluid[6]. Inadequate testosterone levels can cause hypogonadism, characterized by low sperm production, fertility, and reproductive potential. In sexual medicine, testosterone is essential for maintaining libido and erectile function[7,8]. Additionally, adequate testosterone levels support the vascular and neurological systems required to achieve and maintain erections. In terms of sexuality, low testosterone levels have been associated with lower sexual desire, nocturnal erections, and erectile dysfunction, all of which have a substantial influence on quality of life. Testosterone replacement therapy (TRT) is frequently used to address these difficulties, particularly in older men or those with underlying disorders that limit testosterone production[9].

Overall, many factors influence testosterone levels, including age, health conditions, medications, and lifestyle. Maintaining optimal testosterone levels is important for older men to support overall physical and mental health and to reduce the risk of conditions like osteoporosis, metabolic disorders, and cardiovascular diseases.

This narrative review seeks to give a thorough examination of the relationship between testosterone and men's health, with a special emphasis on its physiological, reproductive, and metabolic functions.

It emphasizes the integration of biomarkers with advances in genetic and precision medicine, providing insights into individualized therapy strategies adapted to individual profiles. By combining existing knowledge from several fields, this review emphasizes testosterone's multifaceted impact on health, therapeutic potential, and clinical application issues, with the goal of guiding both clinical practice and future research endeavors.

2 | PHYSIOLOGY OF TESTOSTERONE PRODUCTION

2.1 | Testicular function

The process begins with the conversion of cholesterol into pregnenolone, catalyzed by the enzyme cytochrome P450 side-chain cleavage (P450scc). Pregnenolone is subsequently converted into progesterone by the enzyme 3β-hydroxysteroid dehydrogenase, serving as an intermediate in the pathway leading to testosterone.

One key step involves the enzyme 17α-hydroxylase, which converts progesterone into 17α-hydroxyprogesterone. This intermediate is then transformed into androstenedione by the enzyme 17,20-lyase. The final step of testosterone production occurs when the enzyme 17β-hydroxysteroid dehydrogenase converts androstenedione into testosterone, completing the process in the Leydig cells[10,11].

2.2 | Hypothalamic–pituitary–gonadal (HPG) axis

Testosterone production is regulated by the HPG axis. The hypothalamus releases gonadotropin-releasing hormone (GnRH), which stimulates the anterior pituitary gland to release LH and follicle-stimulating

hormone (FSH). LH directly stimulates the Leydig cells to produce and secrete testosterone[12]. Testosterone levels are regulated through a negative feedback loop. When testosterone levels are high, the hypothalamus reduces the secretion of GnRH, and the pituitary decreases the release of LH and FSH, thereby lowering testosterone production[10,12]. Other factors, such as variations in enzyme activity and overall health, can also influence testosterone production. Testosterone levels typically peak during adolescence and early adulthood, gradually declining with age[10].

2.3 | Development and maintenance of secondary sexual characteristics

Testosterone is essential for the development of secondary sexual traits, which usually appear during puberty. Furthermore, testosterone is required for the growth and maturity of external genitalia, such as the conversion of the prostate's acini into glandular structures after puberty and the enlargement of the penis and scrotum[10,13,14]. Throughout a male's reproductive years, the hypothalamus releases GnRH in pulses every 1–3 h. At puberty, significant changes in hypothalamic and brain activity result in a sharp increase in GnRH secretion, prompting the Leydig cells in the testes to convert cholesterol into testosterone, initiated by LH[10]. Key intermediates in this pathway include dehydroepiandrosterone (DHEA) and androstenedione, precursors mainly produced by the adrenal glands and, to a lesser extent, the testes[15]. DHEA and its sulfated form (DHEA-S) are also metabolized into more potent sex hormones such as testosterone, dihydrotestosterone, and estradiol, which bind to androgen receptors (ARs) and estrogen receptors (ERs) with higher affinity[15]. For testosterone to bind to ARs and exert its effects, it must be in its free form. Only a small fraction remains free and capable of binding to ARs to produce biological effects[9].

2.4 | Regulation of libido and sexual function

Testosterone plays a crucial role in regulating erectile function by increasing nitric oxide (NO) synthesis in penile arteries via endothelial cells and facilitating the release of NO at the synaptic level in non-cholinergic, non-adrenergic nerves[16]. This results in vasodilation and enhanced blood flow, which are essential for initiating and maintaining an erection[17,18]. In addition, testosterone helps maintain the structural integrity of penile tissue and supports spermatogenesis by stimulating Sertoli cells in the testes[19].

Testosterone's influence on sexual function is also seen in its interactions with other hormones. Elevated levels of hormones like prolactin and cortisol can negatively affect sexual function by inhibiting testosterone production or interfering with its action[20,21].

Testosterone has also been shown to improve the efficiency of phosphodiesterase type 5 (PDE5) inhibitors, such as sildenafil, by boosting endothelial function and increasing responsiveness to these medications in men with erectile dysfunction. Recent research has highlighted the efficacy of regenerative medicines, like stem cell therapy and platelet-rich plasma, in treating hypogonadism. These treatments are intended to restore Leydig cell activity, enhance testosterone generation, and address underlying tissue damage[22].

2.5 | Effects of testosterone imbalance

2.5.1 | Hypogonadism

Hypogonadism, characterized by low testosterone levels, affects many men, especially as they age, leading to a variety of symptoms that significantly reduce quality of life. One of the most common and distressing symptoms is sexual dysfunction, which includes decreased libido, erectile dysfunction, and a reduction in spontaneous erections[23].

Hypogonadism can result from disruptions at any stage of testosterone production, whether in the testicles, hypothalamus, or pituitary gland[24]. Testosterone levels naturally decline with age; studies show that hypogonadism affects approximately 10% of men in their 50 s, 20% in their 60 s, and 70% in their 70 s and 80 s[25]. The condition is also associated with obesity and diabetes, as research suggests a correlation between these conditions and lower testosterone levels[24]. Hypogonadism is categorized into two types: primary and secondary.

2.5.2 | Primary hypogonadism

Primary hypogonadism, also known as primary testicular failure, results from problems in the testicles themselves. This condition is common in males with Klinefelter's syndrome, a genetic disorder characterized by an additional X chromosome (XXY). This chromosomal abnormality leads to impaired testicular development and reduced testosterone production[26]. The incidence rate of Klinefelter's syndrome is 9–22 per 10 000 births, but it is often underdiagnosed, with 25%–50% of affected males remaining undiagnosed during their lifetimes [27].

Undescended testicles, a condition where the testicles fail to descend into the scrotum before birth, can lead to primary hypogonadism if untreated. Mumps orchitis, an infection of the testicles by the mumps virus in adolescence or adulthood, is another cause, potentially leading to reduced testosterone levels and long-term testicular damage[28]. Hemochromatosis, an excess of iron in the blood, can also impair testicular function and testosterone production. Furthermore, testicular injuries, due to their sensitivity, can disrupt testosterone production.

Cancer treatments such as chemotherapy and radiation can affect sperm and testosterone production, sometimes resulting in irreversible infertility[29].

2.5.3 | Secondary hypogonadism

Secondary hypogonadism occurs due to problems with the hypothalamus or pituitary gland, which regulates testosterone production. Kallmann syndrome, a condition marked by abnormal hypothalamic development and often linked to anosmia (loss of smell), can cause secondary hypogonadism. The incidence rate of Kallmann syndrome is estimated to be 1:4000 to 1:30 000 male births[27].

Pituitary gland disorders, including tumors, can affect hormone release and testosterone production. Inflammatory conditions like sarcoidosis, histiocytosis, and tuberculosis can impact the hypothalamus and pituitary gland, leading to reduced testosterone levels. HIV/AIDS can also interfere with testosterone synthesis by affecting these brain regions. Certain medications, such as opioid painkillers, can further disrupt testosterone production[30].

Obesity is linked to secondary hypogonadism, possibly due to increased testosterone clearance or inflammation-related hormone imbalances[26]. Stress-induced hypogonadism, resulting from prolonged stress, intense exercise, or weight loss, can also impair hypothalamic function[31].

2.5.4 | Treatment for hypogonadism

The primary treatment for hypogonadism is TRT, which comes in the form of injections, gels, and patches and restores normal testosterone levels. Monitoring is critical for reducing hazards including erythrocytosis and cardiovascular problems[32]. Gonadotropin therapy, including human chorionic gonadotropin (hCG), is used to treat secondary hypogonadism by stimulating natural testosterone production, and is frequently coupled with FSH to preserve fertility. Clomiphene citrate is a non-testosterone option for young men that increases testosterone without impairing fertility. Aromatase inhibitors are useful in cases of excessive estrogen levels because they block testosterone from converting to estrogen. Surgery, such as the removal of a pituitary tumor, can restore hormonal balance in structural reasons[33,34].

2.5.5 | Hypergonadism

Hypergonadism, sometimes referred to hyperandrogenism, refers to the overproduction of sex hormones, particularly testosterone, in men. This excess of testosterone can result from various underlying conditions, including cancers, genetic disorders, and hormonal imbalances. The causes of hypergonadism include gonadal tumors, excessive secretion of adrenocorticotropin (ACTH) in 32-hydroxylase deficiency (congenital adrenal hyperplasia [CAH]), adrenal tumors, exogenous androgen use, and central precocious puberty. Gonadal tumors, such as Leydig cell tumors in the testes, can produce excess testosterone and may be benign or malignant[35]. The use of exogenous androgens, including anabolic steroids or testosterone supplements, can also result in hypergonadism. In boys, central precocious puberty, where early activation of the HPG axis occurs, can lead to premature puberty and elevated testosterone levels[10].

Symptoms include early onset of puberty in boys, increased libido, hirsutism (excessive body hair), acne, rapid growth, aggressive behavior, and infertility due to reduced normal sperm production[36].

Diagnosis involves assessing symptoms and measuring serum testosterone levels through blood tests. Imaging studies, such as MRIs or ultrasounds, are conducted to detect tumors or abnormalities. Genetic testing can help identify any underlying genetic disorders. The primary goal of treatment is to manage symptoms and address the root cause[37].

Treatment options include medications that block or reduce testosterone production, surgical removal of tumors, radiation therapy to shrink hormone-producing tumors, and lifestyle changes to control symptoms[38]. Regular monitoring and follow-up with healthcare providers are essential to adjust treatment plans and address any side effects or complications.

2.5.6 | Treatment for hypergonadism

Anti-androgen medicines, such as flutamide or spironolactone, mitigate the consequences of high testosterone, particularly in androgen-secreting tumors. Gonadotropin-releasing hormone (GnRH) analogs reduce testosterone production in circumstances such as premature puberty. In severe or resistant cases, androgen-producing tumors may need to be surgically removed, or an orchiectomy performed. Hormonal therapy such as estrogen or progestin can help women with hyperandrogenism manage their symptoms, especially in PCOS situations. Lifestyle adjustments and psychological support are essential adjuncts to managing symptoms and improving outcomes, especially in younger patients or those with long-term problems[38,39].

2.6 | Testosterone replacement therapy (TRT)

2.6.1 | Types of testosterone therapy

Although various types of testosterone therapy are available, each with its own benefits and side effects (Figure 1, Table 1), lifestyle changes remain the first step

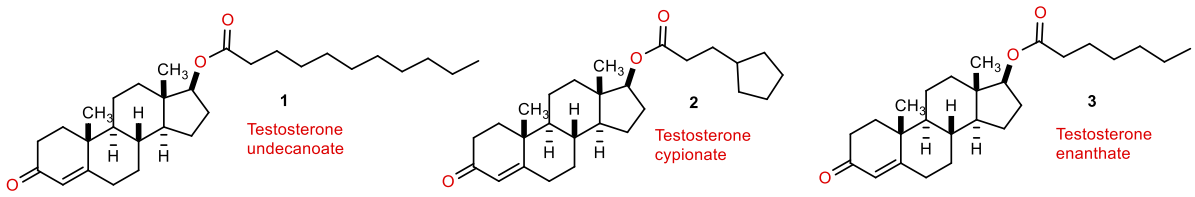

FIGURE 1 Testosterone esters used in therapy: undecanoate (1), cypionate (2), enanthate (3).

TABLE 1 Testosterone preparations for replacement therapy according to European Association of Urology guidelines.

Formulation	Administration	Advantages	Disadvantages
Testosterone undecanoate	Oral; 2–6 cps every 6 h.	Absorbed through the lymphatic system, with consequent reduction of liver involvement.	Variable levels of testosterone above and below the mid-range. Need for several doses per day with intake of fatty food.
Testosterone cypionate	Intramuscular; one injection every two to three weeks.	Short-acting preparation that allows drug withdrawal in case of onset of side-effects.	Possible fluctuation of testosterone levels.
Testosterone enanthate	Intramuscular; one injection every two to three weeks.	Short-acting preparation that allows drug withdrawal in case of onset of side-effects.	Fluctuation of testosterone levels.
Testosterone undecanoate	Intramuscular; one injection every ten to fourteen weeks.	Steady state testosterone levels without fluctuation.	Long-acting preparation that cannot allow drug withdrawal in case of onset of side-effects.
Transdermal testosterone	Gel; daily application.	Steady-state testosterone level without fluctuation.	Risk of interpersonal transfer.
Subdermal depots	Subdermal implant every five to seven months.	Long duration and constant serum testosterone level.	Risk of infection and extrusion of the implants.

in treating hypogonadism. Niskanen et al. reported that a low-calorie diet for a few weeks can increase free testosterone levels and promote weight loss[40].

Oral testosterone preparations, despite their convenience, are generally not used for treating hypogonadism due to significant drawbacks, including liver toxicity, poor bioavailability, and a short duration of effect. Hepatotoxicity is a notable side effect associated with oral testosterone due to its metabolism in the liver[41]. A newer formulation, testosterone undecanoate (Jatenzo™), is FDA-approved and absorbed via the lymphatic system, thereby avoiding liver issues. However, it must be taken with fatty meals. Intramuscular testosterone preparations, such as testosterone cypionate (Depo-Testosterone), testosterone enanthate, and testosterone undecanoate (Aveed™), are administered via injection typically every 10 weeks. These have more stable levels with less frequent peaks and troughs but can still have supraphysiologic peaks and subphysiologic troughs.

Subcutaneous pellets, administered every 4–7 months, offer long-term hormone release but require a minor surgical procedure and have a 5%–10% risk of infection[41]. Transdermal preparations include patches and gels. Patches may cause skin irritation, while gels carry a risk of transmission through contact. Newer gel formulations, such as those applied to the axilla, reduce transmission risk by avoiding contact areas[41]. Transdermal gels offer the advantage of daily application, mimicking circadian rhythm, and providing steady hormone levels with long-term effects, which include increased total testosterone and estradiol (E2), and decreased LH, FSH, and SHBG[42]. Nasal preparations, like Natesto™, reduce skin contact transmission risk but require application three times daily into each nostril, which can be less convenient[43]. Buccal preparations, such as gum or a putty-like substance, are applied twice daily and absorbed through the buccal mucosa, but may cause gum bleeding, mouth irritation, and taste alterations[41].

TRT provides several clinical benefits, including reductions in fat mass, increases in lean mass and strength[44], improvements in lipid profiles and glucose metabolism[41], and decreases in inflammatory markers such as C-reactive protein (CRP)[45]. Additionally, TRT helps alleviate lower urinary tract symptoms (LUTS), increases bladder volumes, and enhances bone density[46]. Additionally, TRT contributes to better sexual function[47], improved mood and overall feelings of well-being[44], and reduced depression[41]. However, TRT can

have some negative effects, including polycythemia, new or worsening congestive heart failure (CHF), fluid retention, exacerbation of obstructive sleep apnea (OSA), acne, and testicular atrophy[48,49].

2.6.2 | Biomarker-based diagnosis

Recent advances in biomarker research have revolutionized the identification and treatment of testosterone-related disorders. Traditional markers such as SHBG, LH, and free testosterone continue to provide useful information about androgen status in addition to total testosterone measures. Innovations such as liquid chromatography-mass spectrometry (LC-MS) have improved diagnostic precision, notably for detecting low testosterone levels in disorders like hypogonadism[50].

Emerging biomarkers, such as insulin-like factor 3 (INSL3) and testosterone-to-estradiol ratios, have shown potential in stratifying patients for targeted therapeutic approaches. Furthermore, advances in proteomic and genomic analysis allow for the identification of individual variations in testosterone metabolism, which supports tailored diagnostic procedures[51]. These results emphasize the growing importance of biomarker-based diagnostics in testosterone-related healthcare and patient outcomes.

2.6.3 | Biomarkers in TRT

Biomarkers are critical for improving TRT, assuring efficacy and safety. Core indicators such serum total testosterone, free testosterone, and SHBG remain important for therapy monitoring. Emerging biomarkers, like INSL3, which gives a consistent measure of Leydig cell function, provide further diagnostic depth, especially in circumstances were changing testosterone levels complicate assessment[52].

TRT's systemic effects are increasingly being evaluated using metabolic and cardiovascular health markers such as adiponectin, CRP, and lipid profiles. Hematological indicators, such as hemoglobin and hematocrit, are also important for detecting concerns like erythrocytosis[53].

Innovative genomic and proteomic technologies improve TRT by revealing genetic variations in AR sensitivity and testosterone metabolism, allowing precision medicine methods. LC-MS technology improves the precision of biomarker detection, allowing for more accurate therapeutic changes[54]. These advances in biomarker research ensure that TRT procedures are safer, more successful, and suited to specific patient needs, making biomarker integration a critical component of individualized testosterone therapy.

2.6.4 | Testosterone and aging

Aging significantly impacts the male HPG axis, which regulates testosterone secretion and production. As men age, there is a net decline in sperm and testosterone output and this, in part, to reduced pituitary gonadotropin output of LH, caused by diminished hypothalamic secretion of GnRH[55]. Leydig cells in the testes become less responsive to LH stimulation compared to younger men. Consequently, older men have lower circulating serum total testosterone levels, and the typical rise in LH levels associated with primary hypogonadism is attenuated[56].

Approximately 50% of men in their 80 s and 40% of men over the age of 45 have hypogonadism[57]. After the age of 30, testosterone levels decrease by about 100 ng/dL every decade, or at an average rate of 1%–2% per year, though this rate may vary depending on factors such as obesity, drug use, and chronic illness[58]. Additionally, SHBG strongly, which is increasing by aging, binds circulating testosterone, creating an inverse relationship between serum SHBG and free testosterone levels in older men[59,60]. Precision medicine's involvement in identifying patients at higher risk for testosterone decline, using genetic profiling to anticipate age-related hormonal changes, resulting in more tailored treatment methods for testosterone deficiency[61].

2.6.5 | Testosterone and metabolic health

Obesity leads to increased secretion of inhibin, which inhibits testosterone production. Precision medicine's involvement in identifying patients at higher risk for testosterone decline, using genetic profiling to anticipate age-related hormonal changes, resulting in more tailored treatment methods for testosterone deficiency[62]. The obesity paradox highlights that moderate body fat may provide a protective effect in CVD and heart failure patients[63].

Testosterone also improves insulin sensitivity and reduces insulin resistance by enhancing insulin receptor signaling pathways. It stimulates myogenesis and muscle hypertrophy by promoting protein synthesis and reducing protein breakdown[64]. Additionally, testosterone influences adiponectin production by binding to ARs, with low testosterone levels correlating with low adiponectin levels, particularly in hypogonadal men[65].

Furthermore, the aromatase enzyme converts testosterone into 17β-estradiol, which activates estrogen receptors (ERα and ERβ). Activation of ERα can lead to visceral fat accumulation and insulin resistance, while ERβ promotes fat browning and energy expenditure, counteracting the effects of ERα[66].

2.6.6 | Testosterone and cardiovascular health

One key pathway involves the activation of the growth arrest-specific gene 6 (GAS6), which has a pro-survival effect on vascular smooth muscle cells (VSMCs)[67]. Genomics has demonstrated that mutations in the GAS6 gene can effect cardiovascular health, underlining the precision medicine approach to customizing testosterone therapy[68].

Testosterone also reduces atherosclerosis by modulating immune responses, exhibiting anti-inflammatory properties. It lowers the expression of pro-inflammatory cytokines such as NF-κB, interleukin (IL)-1β, and IL-6, while promoting the anti-inflammatory cytokine IL-10[69].

Testosterone enhances cardiac function via AR-mediated mechanisms, improving myocardial contraction and relaxation, particularly with aging. It inhibits cardiomyocyte apoptosis and fibrosis, offering anti-ischemic protection. The AR pathway also activates AMPK, promoting mitochondrial biogenesis and autophagy, ensuring cellular health. Recent trials employ genetic testing to identify individuals most likely to benefit from testosterone therapy's effects on the AMPK pathway, providing a precision medicine approach to cardiovascular protection[70,71].

2.6.7 | Testosterone and bone health

Testosterone, the most abundant bioactive sex hormone, exerts its effects through AR binding, which facilitates the synthesis of dihydrotestosterone (DHT) and estradiol. These molecules are essential for bone development, particularly during adolescence[64]. The use of TRT in osteoporosis is further supported by a more thorough understanding of the intracrine activities of sex steroids in bone tissue made possible by advanced imaging technology and genomic data[72]. Understanding the intracrine actions of sex steroids is crucial for developing treatments for bone-related conditions. For example, TRT has been shown to increase bone mineral density (BMD) and reduce fracture risk in hypogonadal men[64,73]. By finding biomarkers for the best possible therapy results, precision medicine techniques have improved our knowledge of how each person reacts to TRT in terms of bone density and fracture risk[74].

2.6.8 | Testosterone and mental health/ Alzheimer's disease

Low testosterone levels are strongly linked to mood disorders, particularly depression and anxiety. Men with hypogonadism, characterized by reduced testosterone production, are more prone to depressive symptoms compared to those with normal testosterone levels[75,76]. Testosterone's impact on mood involves complex interactions with various neurotransmitters. It modulates serotonin activity, a neurotransmitter associated with mood and well-being[77,78]. Testosterone promotes cognitive function, particularly memory and executive functions, and higher levels have been associated with improved performance on spatial and memory tasks. Decreased testosterone in aged males has been linked to an increased risk of cognitive impairments like Alzheimer's disease. Furthermore, testosterone may protect the brain by reducing oxidative stress and inflammation, both of which are linked to neurodegeneration. It has also been linked to reduced amyloid-beta accumulation, which is a major feature in Alzheimer's disease pathology and may minimize the likelihood of cognitive decline[79,80]. Precision therapies based on targeted genetic manipulations have helped identify patient subgroups most likely to benefit from testosterone therapy, opening up new treatment options for Alzheimer's disease. Furthermore, recent research using genetic profiles and biomarkers has shown how individual genetic variables influence testosterone's effects on mood, paving the path for tailored treatment options for depression and anxiety[81].

2.6.9 | Testosterone and prostate health

Testosterone's role in prostate health has been debated, particularly regarding prostate cancer and benign prostatic hyperplasia (BPH). Historically, high testosterone levels were believed to increase prostate cancer risk due to its androgen dependency, but recent studies suggest low testosterone may link to aggressive cancers[82,83]. In evaluating when testosterone replacement therapy (TRT) is suitable and safe for individuals with prostate health concerns, precision medicine techniques are being utilized to more accurately assess prostate cancer risk. These efforts include genetic markers and PSA test[62].

The “saturation model” proposes that prostate tissue becomes saturated at low testosterone levels, making further increases unlikely to elevate cancer risk. Evidence shows TRT does not increase prostate cancer risk and may improve LUTS, regardless of prostate size[84,85]. Monitoring through PSA tests and digital rectal exams remains essential for detecting prostate abnormalities during TRT[86]. New genetic markers, such as single-nucleotide polymorphisms (SNPs) in androgen receptor genes, have shown promise in identifying those at increased risk of developing prostate cancer[87]. Variations in genes like *CYP17A1*, involved in testosterone production, may further understand the complex interaction between testosterone levels and prostate cancer susceptibility[88].

2.6.10 | Testosterone and reproductive health

Low testosterone levels can impair spermatogenesis, leading to reduced sperm count and quality. Conditions like hypogonadism are often associated with oligospermia (low sperm count) or azoospermia (absence of sperm), both contributing to male infertility. Restoring normal testosterone levels in men with hypogonadism can improve sperm production, though recovery extent varies[89]. Testosterone has also been explored as a potential male contraceptive. High doses of exogenous testosterone can suppress the HPG axis, reducing LH and FSH levels, which in turn decreases endogenous testosterone production and spermatogenesis, lowering sperm count to infertile levels[90,91].

2.6.11 | Artificial intelligence (AI) and testosterone therapy

AI tools hold significant promise in predicting the outcomes of TRT, particularly by analyzing a wide array of patient data. AI models, including machine learning algorithms, can integrate clinical factors such as baseline testosterone levels, comorbidities, age, and response to previous treatments to predict the efficacy of TRT for individual patients. Research shows that AI-driven predictive models can improve personalized treatment plans by identifying patterns in large data sets, which may not be evident through traditional clinical assessment alone[92]. For example, AI can forecast which patients are most likely to experience improvements in symptoms like fatigue or sexual dysfunction and which might be at risk for side effects such as prostate enlargement or cardiovascular issues[93].

In addition to clinical outcomes, AI technologies have been utilized to optimize the timing, dosage, and frequency of TRT administration, resulting in better patient outcomes and fewer dangers. Machine learning technologies, when combined with biomarkers and genetic information, can improve long-term therapy success predictions, resulting in a more tailored approach to hormone replacement therapies[93]. This could be especially effective in managing the variation in testosterone levels observed among patients and predicting possible problems such as hypergonadism or exacerbation of pre-existing health conditions[94].

2.6.12 | Future perspectives

The role of testosterone in health remains a promising area for study and clinical development. Precision medicine techniques are predicted to alter testosterone-related therapy by enabling personalized treatment plans based on genetic, hormonal, and lifestyle factors. Emerging technologies, like genetic testing and enhanced biomarker analysis, may aid in the identification of patient subgroups who will benefit the most from testosterone replacement treatment. Furthermore, the development of innovative therapeutic compounds that target androgen receptors or imitate testosterone's actions without causing adverse effects may improve treatment outcomes for disorders such as hypogonadism, prostate health concerns, and cognitive decline. Longitudinal research and real-world data integration will be critical in determining the long-term benefits and hazards of TRT and other testosterone-based treatments.

2.7 | Limitations

Despite improvements, TRT research still has serious limitations. Current studies are hindered by small sample sizes, short follow-up periods, and varied designs, limiting the generalizability of their conclusions. Additionally, there is little agreement on the appropriate testosterone levels, particularly for the elderly or those with comorbidities. TRT use is further complicated by ongoing safety concerns, including those related cardiovascular risks, prostate cancer development, and fertility. Non-medical testosterone use for anti-aging or performance improvement raises ethical considerations. Future large-scale, well-designed trials, as well as multidisciplinary research in endocrinology, cancer, and reproductive medicine, are critical for defining the risks and benefits of TRT and improving therapeutic decisions.

3 | CONCLUSION

Testosterone's influence extends beyond sexual differentiation and secondary male characteristics to impact metabolic, cardiovascular, and reproductive systems. While testosterone levels naturally decline with age, this process is highly individualized. Abnormal fluctuations in testosterone levels, whether excessive or insufficient, are associated with conditions ranging from hypogonadism to an increased risk of chronic diseases. Understanding these dynamics is essential for developing targeted therapies. Continued research into testosterone's complex interactions within the body will provide deeper insights into its role. Precision medicine advancements now allow for more customized approaches to testosterone therapy, maximizing benefits while minimizing risks. AI methods, like machine learning models, are also emerging as significant assets in forecasting testosterone therapy outcomes, giving more tailored treatment plans. Despite promising findings, there are still issues in reconciling therapeutic efficacy with safety concerns, particularly for long-term results.

Continued study is critical for completely understanding testosterone's multifaceted role and refining therapy techniques for better health outcomes.

AUTHOR CONTRIBUTIONS

The conceptualization of the study was carried out by Aksam Yassin and Raed M. Al-Zoubi. The methodology was developed by Raidh Talib Alzubaidi, Hatem Kamkoum, Khalil Garada, Ayman A. Zarour, and Mai Elaarag. Data collection was performed by Khalil Garada, Ayman A. Zarour, Mai Elaarag, Ahmad R. Al-Qudimat, and Zainab E. Fares. Manuscript preparation was handled by Khalil Garada, Ayman A. Zarour, Mai Elaarag, Ahmad R. Al-Qudimat, and Zainab E. Fares. Writing, review, and editing were conducted by Raed M. Al-Zoubi, Raidh Talib Alzubaidi, and Hatem Kamkoum, while the final writing, review, and editing were completed by Aksam Yassin, Raed M. Al-Zoubi, and Abdulla A. Al-Ansari. All authors have read and agreed to the published version of the manuscript.

ACKNOWLEDGMENTS

The publication of this article is funded by the Qatar National Library.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings in this study are available from the corresponding authors upon reasonable request.

ETHICS STATEMENT

Not applicable.

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