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REVIEW

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Aging, testosterone and male fertility therapy: a review

Yeonhee Pyo[1], Ki Han Kwon[2,*]

[1]Department of Beauty Cosmetics, College of Biomedical and Health Science, Konkuk University, 27478 Chungju, Republic of Korea
[2]College of General Education, Kookmin University, 02707 Seoul, Republic of Korea

***Correspondence**
kihan.kwon@kookmin.ac.kr
(Ki Han Kwon)

Abstract

Men's fertility declines as they age. Reduced reproductive function lowers testosterone levels, which leads to poor sperm quality and low fertility. This article summarizes the decline in male fertility and reproductive functions with age and highlights the relationship between aging and testosterone. It also examines various testosterone-based health treatments that can improve male fertility. A systematic search was conducted in five databases, including PubMed, SCOPUS, Google Scholar, Web of Science and EMBASE. The search terms included "male aging", "male fertility", "male fertility treatment", "testosterone" and "fertility treatment". We systematically reviewed primary English-language studies, including peer-reviewed and non-peer-reviewed sources, while excluding samples, reviews, internet articles, editorials, protocols, perspectives, commentaries, publications, reports and non-primary data. We also manually searched reference lists. It was observed that testosterone impacts male virility, physical and mental health, and the aging process. Novel therapeutic approaches, such as the use of natural product-derived pharmacologic therapies are required to maintain healthy gonadal function, or enhanced reactive oxygen species (ROS) scavenging and sperm quality while considering gene and DNA repair.

Keywords

Male aging; Male fertility; Testosterone; Male reproduction

1. Introduction

The steroid hormone, androgens especially testosterone, are known to have a positive impact on the quality of life and longevity of men. Testosterone binds to androgen receptors and affects various systems in the body, such as the muscle and adipose tissue, skeletal, cardiovascular, immune and nervous systems. With aging, the levels of testosterone in their bodies decline [1]. The exact cause of male aging is still unknown, but it is believed to result from a decrease in nicotinamide adenine dinucleotide (NAD) levels. This decrease is associated with low hormone production and testicular volume, which declines sperm quality [2]. Thus, gonadal function is important for the longevity of a man's health. As men get older, their testicular volume and gonadal function tend to decrease [3, 4]. Late-onset hypogonadism (LOH), is accompanied by various symptoms such as loss of libido, erectile dysfunction, increased visceral fat, anemia, depression, sweating, flushing, metabolic syndrome, decreased energy, muscle mass, and bone density [5]. LOH also reduces the levels of NAD, which is a coenzyme form of nicotinamide adenine dinucleotide (NAD^+) [6–8]. Abnormal levels of NAD variants, including nicotinamide adenine dinucleotide (NADH), $NADP^+$ and nicotinamide adenine dinucleotide phosphate (NADPH), are crucial for metabolic and energy-regulating biochemical reactions. If these levels are disrupted, reactive oxygen species (ROS) are produced and glutathione (GSH) is depleted, resulting in a deteriorated oxidative environment in the testis [9]. Testosterone replacement therapy (TRT) is a potential treatment for male aging by improving the symptoms of LOH. However, appropriate use of this therapy requires a thorough understanding of LOH's pathological features and its effectiveness in preventing organismal aging [10]. Serum testosterone levels are linked to aging in men, and total testosterone levels are crucial for male homeostasis, providing new insights into age-related diseases and homeostasis biomarkers [11]. In contrast to women, men do not experience menopause, but their fertility gradually decreases with aging [12]. Male fertility depends on the development and maintenance of germ cells and, ultimately, the production of healthy sperm. It is associated with the physiological health of mitochondria, which play a crucial role in the male reproductive system [13, 14]. Mitochondria produce energy and participate in important cellular processes such as apoptosis and calcium homeostasis [15]. Mitochondrial physiological disorders can decrease male fertility and impact oxidative stress [16]. Decreased testosterone activity due to excessive adipose tissue leads to mitochondrial dysfunction. Oxidative damage to lipids, proteins, and mitochondrial DNA (mtDNA) decreases the saturated fat (SFA) score [17]. SFAs, which are included in polyunsaturated fatty acids (PUFAs), play a significant role in sperm sensitivity and fertility. To preserve sperm function and fertility, it is essential to maintain a proper balance of ROS and antioxidants [18, 19]. A healthy reproductive system in men can be achieved through a regular

lifestyle and proper exercise. It is crucial to manage male fertility because low testosterone levels can cause infertility. Proper exercise and a regular lifestyle can help reduce pro-inflammatory cytokine levels, improve steroid production, spermatogenesis and semen quality, all of which are linked to male fertility [20].

This article aims to analyze the factors related to male aging and their impact on male fertility. It highlights the crucial role of testosterone in maintaining a healthy male reproductive system. The review also covers treatments for male fertility issues and ways to increase testosterone levels in older men.

2. Methods

In December 2023, we conducted a literature search for our review using five databases: PubMed, SCOPUS, Google Scholar, Web of Science and EMBASE. The search strategies used were "male aging", "male fertility", "male fertility treatment", "testosterone" and "fertility treatment".

We searched above mentioned databases using free text and title search terms, to ensure we retrieved all studies related to male aging and male fertility treatment. From the identified studies, we removed duplicates and unidentified studies and reviewed the abstracts of the remaining literature. Two reviewers screened all titles and abstracts to identify eligible studies. Two researchers independently screened the full text of eligible studies using the same criteria listed above. We performed pre- and post-eligible expert citations to capture all relevant studies by manually searching reference lists using Scholarly Search Alert. We noted reasons for exclusion during the expert screening phase.

Our database search returned 6268 studies. After removing duplicates, 1307 studies remained. After title and abstract screening, we excluded 4961 studies. We assessed the eligibility of 104 full-text articles and excluded studies of women's fertility, women's disease treatment, or studies that were not related to men. Finally, we included seven studies in our systematic review (Fig. 1).

3. Results

3.1 Testosterone and male aging

Testosterone helps to maintain physical and mental health in men. Aging and testosterone are closely linked, and as testosterone levels decline, men become more prone to obesity, angina, dementia, arteriosclerosis and metabolic syndrome [21]. Low testosterone levels are associated with LOH, and increasing testosterone levels in patients with LOH can improve their quality of life (QOL) [22]. In men, testosterone levels continue to rise until the age of 20 and then gradually decline. Changes become apparent after the age of 35 when semen volume, total sperm count, sperm motility, and normal morphology are compared [23–25]. Additionally, 2–5% of men in their 40s and 30–70% in their 70s experience declining testosterone levels. This decline decreases the quantity of Leydig cells, the secretion of testosterone by the testes, and the secretion of gonadotropin-releasing hormone (GnRH), all of which contribute to physical aging [26, 27]. Testosterone levels are closely associated with fat cells. Men with obesity tend to have excessive aromatase activity, which increase the conversion of testosterone to estradiol [28]. This activity inhibits the hypothalamic-pituitary-gonadal axis and reduces testosterone secretion from the testes. Leptin, a protein secreted by adipocytes, plays a role in regulating food and energy in men [29] and has an inverse correlation between luteinizing hormone (LH) stimulation and androgens. It inhibits LH by blocking the secretion of luteinizing hormone-releasing hormone (LHRH) from visceral adipose tissue, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) [30, 31].

Obesity is a well-known risk factor for cellular senescence [32]. It accelerates aging and inhibits testosterone synthesis in Leydig cells, which are an important component of the aging mechanism. This is due to a decrease in testosterone (Fig. 2) [33]. Obesity also reduces telomere length and increases epigenetic aging, which further accelerates aging [34]. These findings are in line with the findings who discovered that oxidative stress and inflammation activate the p38 mitogen-activated protein kinase (p38 MAPK) pathway [35]. This pathway is involved in aging and obesity by shortening telomere length and is associated with epigenetic aging and DNA damage [36]. The ROS/MAPK pathway, which is a signaling modulator, exerts anti-apoptotic and anti-autophagic activity and inhibits MARKs in inflammation and cytokine expression [37]. This encourages responses necessary to mitigate cellular damage, thus preventing chronic diseases such as diabetes, cardiovascular disease, inflammatory bowel disease, atherosclerosis, and neurodegenerative disorders [38, 39]. The involvement of oxidation and inflammation in Leydig cells is also linked to obesity in the aging mechanism [40]. Several endogenous and exogenous processes produce reactive oxygen and nitrogen species (RONS), and oxidative stress occurs when RONS production and antioxidant defense are out of balance. Aging is defined by a gradual loss of function in tissues and organs, and oxidative stress is linked to age [41]. Obesity leads to oxidative stress and cellular aging [42]. Animal studies have shown that diet-induced stress and inflammation contribute to the activation of p38, and that diet-induced oxidative stress and inflammation can lead to premature aging [43–45].

As men age, the frequency of sexual intercourse tends to decrease, and sexual discomfort tends to increase. This may be attributed to erectile dysfunction or sexual hormone problems [46]. With age, serum testosterone levels decrease, and behavioral changes in partner relationships and social status affect libido, sexual motivation, and spontaneous erections, leading to decreased sexual desire and erectile dysfunction [47]. Testosterone deficiency can cause decreased semen quality, chronic diseases (depression, cardiovascular disease, diabetes and sexual dysfunction) [48], and changes in the semen metabolome and sperm proteome. This has been analyzed by a biomarker panel consisting of metabolites of Pipamperone, 2,2-bis(hydroxymethyl)-2,2′,2′-nitrilotriethanol, Arg-Pro, and Triethyl phosphate [49]. Clinical prescribing and dosing routes should be explored to minimize side effects [50, 51].

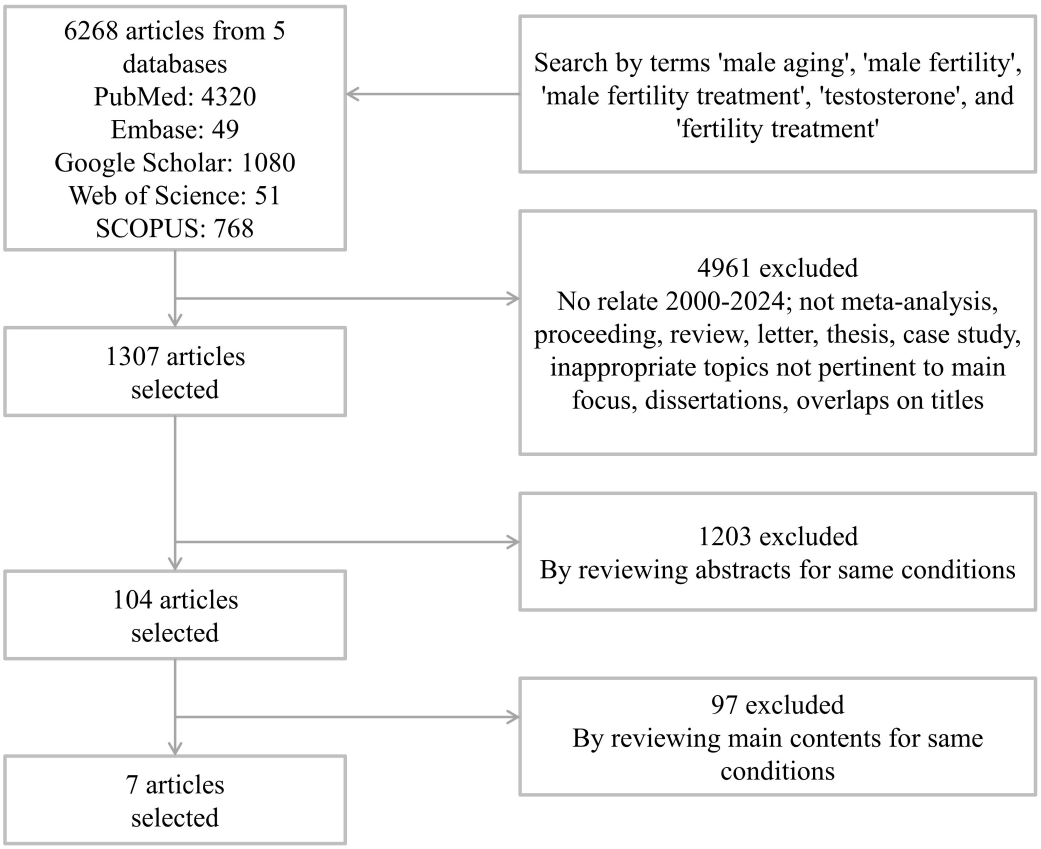

FIGURE 1. Review process for systematic reviews.

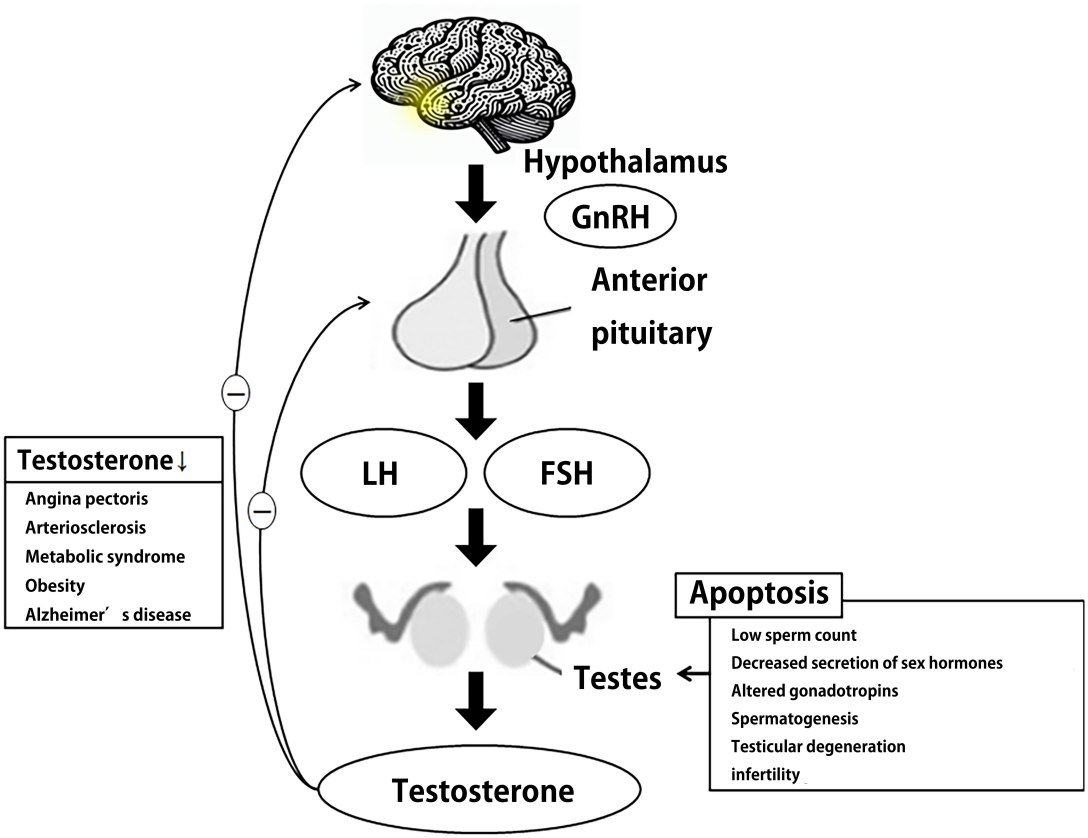

FIGURE 2. Decreased male fertility due to low testosterone. GnRH: Gonadotropin-releasing hormone; LH: Luteinizing hormone; FSH: follicle stimulating hormone.

3.2 Testosterone affects male fertility

Testosterone is a vital hormone for men's physical and mental health. A decline in testosterone levels can lead to various diseases, such as such as angina, atherosclerosis, metabolic syndrome, obesity and dementia [52]. It also results in reduced sperm count, testicular cell death, and decreased hormone secretion, leading to infertility [53, 54]. The decrease in testosterone levels can negatively affect other cells, such as Sertoli cells, Leydig cells, germ cells, and the hypothalamic-pituitary-testicular axis [55]. Endocrine-disrupting chemicals (EDCs) can also have negative effects on men's health and fertility by interfering with the body's natural hormones [56]. Prenatal exposure to EDCs can cause congenital penile abnormalities such as hypospadias, cryptorchidism or testicular cancer. Dichlorodiphenyldichloroethylene (p,p′-DDE) an anti-androgenic chemical, which inhibits the function of the hypothalamic pituitary-testicular axis and androgen biosynthesis, ultimately leading to reduced testosterone levels and impaired spermatogenesis [57]. Prolonged exposure to EDCs can inhibit the estrogen sulfotransferase and aromatase enzymes, leading to an increase in estrogen levels [58–60]. This increase in estrogen levels can lead to toxic effects on the male reproductive system, particularly the testes and genitals. Germ cells expressing compounds like 1,2-Dibromo-3-chloropropane (DBCP) can cause birth defects in spermatogenesis, ultimately leading to male reproductive system problems such as impaired reproductive function, long-term reproductive disorders, low testicular function, poor semen quality, hypospadias, congenital penile abnormalities, and testicular cancer [61, 62].

Testosterone production is stimulated by follicle-stimulating hormone (FSH) and luteinizing hormone (LH) by Leydig cells, which act on gonadal receptors [63]. However, high levels of testosterone in the blood can affect the pituitary gland's ability to respond to gonadotropin releasing hormone (GnRH) stimulation, which reduces hypothalamic GnRH release [64]. This can lead to decreased activity levels of testicular steroidogenic enzymes (3β- and 17β-hydroxysteroid dehydrogenases), and a reduction in daily sperm count, epididymal sperm count, sperm motility, sperm viability, hypo-osmotic swelling (HOS) tail-coiled spermatozoa, and decreased mRNA expression levels of steroidogenic acute regulatory protein (StAR) and circulating testosterone. The relationship between testosterone and male fertility is illustrated in Fig. 3 [65].

3.3 Testosterone replacement therapy

TRT has many potential benefits for men with low testosterone levels [66, 67]. It can improve bone health by increasing bone mineral density and bone health markers [68–70]. It can reduce cardiovascular diseases [71, 72], and prevent lower urinary tract symptoms (LUTS) which can lead to additional health problems like urinary incontinence, urinary tract infections, and bladder problems [73, 74]. In addition, TRT can address mental health issues, including depression, despondency, anger, and cognitive impairment in those over 70 years of age due to androgen imbalance [75–78].

A clinical trial focusing on TRT for male aging showed that TRT had a bone mineral density (BMD) benefit compared to placebo after 12 months of treatment in testicular cancer survivors (TCS) with a deficiency of 69 mild Leydig cells. This clinical evidence of procollagen type 1 N-terminal propeptide (P1NP), a bone biomarker, indicates the value of testosterone as a standard treatment option [79]. However, in men aged 55–67 years, TRT treatment was associated with a higher incidence of prostate cancer (PCa) and higher mortality from all causes of cardiovascular disease (CVD) compared to no treatment in 78,615 subjects in the Prostate Cancer Randomized Screening Study. Therefore, blood testosterone levels have been discussed as a way to identify and determine cancer risk [80]. A study conducted in China on 270 men aged between 20 and 70 years confirmed a link between aging and testosterone, indicating a gradual reduction in calculated free testosterone (cFT) levels with age [81]. The use of routine TRT to improve metabolic health is also encouraged in patients with Leydig cell deficiency, as demonstrated by clinical examples from randomized controlled trials. After 12 months of transdermal TRT or placebo treatment, it showed no statistically significant difference in 2-hour glucose and insulin. However, glucose and insulin effects were observed with 12 months of TRT, leading to improvements in insulin [82]. A trial of testosterone undecanoate (TU) in 138 hypogonadal men with an average age of 54 years showed an improvement in ambulatory blood pressure (ABP) after a 4 months of treatment. It can help predict BP increases in response to testosterone therapy [83]. Also, a randomized, placebo-controlled trial in obese 83-year-old men found that testosterone treatment attenuated weight loss in muscle mass and hip bone mineral density (BMD), which may improve aerobic capacity [84]. Furthermore, TRT has a positive effect on male anemia. A clinical trial found that TRT is more effective than placebo in correcting anemia in middle-aged and older men with hypogonadism and anemia. Even in the absence of anemia, treatment with TRT has been reported to be associated with a lower incidence of pernicious anemia compared to placebo [85]. Table 1 summarizes clinical examples of TRT.

4. Discussions

Sexual dysfunction, endocrine disorders, lifestyle factors such as tobacco use, anatomical factors, and aging, all of which are related to semen and have an empirical impact on life, account for 30–50% of male infertility cases [86]. Fatigue, decreased libido, depression, and sleep disturbances are some of the symptoms. These can be improved with TRT treatment. As a result, new potential male therapies based on natural products and functional foods are emerging, offering safe treatments and supplements [87]. Herbs, spices, and plant-derived extracts can boost testosterone levels in men. Fenugreek seed extract, ashwagandha root extract, and leaf extract have all been shown to raise testosterone levels in men, as have Asian red ginseng and forskolin root extracts [88]. Panax ginseng can benefit male sperm health by protecting against inflammatory responses and improving reproductive function in animal models of reproductive dysfunction caused by D-galactose from ginseng stem-leaf saponins (GSLS). GSLS can significantly increase testosterone levels, decrease cortisol, FSH and LH levels, and inhibit mitogen-activated protein

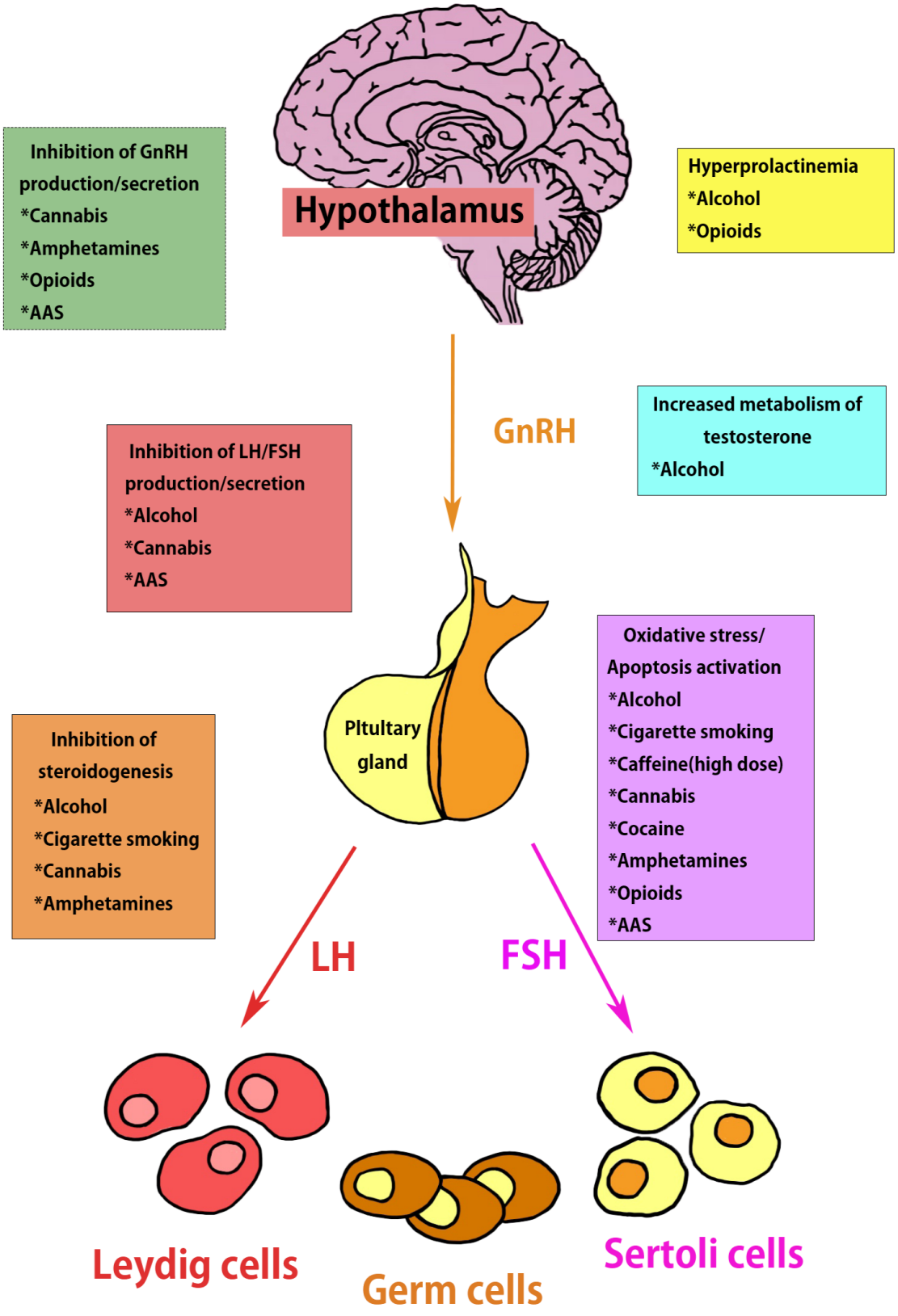

FIGURE 3. The main mechanisms may decrease testosterone levels and sperm. Substance or drug abuse can lower testosterone levels and decrease sperm production through various mechanisms. These include the inhibition of GnRH production and secretion, an increase in prolactin levels, inhibition of gonadotropin production and secretion, inhibition of steroidogenesis, an increase in testosterone metabolism, oxidative stress, and induction of apoptosis. Some abbreviations used in this context: AAS: for anabolic-androgenic steroids; FSH: follicle-stimulating hormone; GnRH: gonadotropin-releasing hormone; LH: for luteinizing hormone.

TABLE 1. Clinical case study on TRT as a treatment for men.

Subjects	Setting	Findings	Reference
270 men in China (Beijing, Shanghai, Xi'an, Chongqing) Healthy, substance-addicted and mentally ill adults living independently	Randomized study, controlled trial	Serum total testosterone values do not decrease with aging, while the level of cFT decreases progressively with aging. Prevalence of androgen deficiency: less than 15% before age 50, 30% thereafter, 45% after age 70.	J-Y Li *et al.* [81]
TCS: 69 (TRT = 35, placebo = 34)	Randomized double-blind trial	TRT did not change BMD, no difference in CTX, but significantly increased P1NP (11.65 µg/L).	Jørgensen *et al.* [79]
78,615 men ages 55–67	Randomized study of screening	No association with increased risk of PCa in men using TRT, but no increased mortality from PCa, CVD compared to non-users.	Siltari *et al.* [80]
TCS = 69 (TRT = 35, placebo = 34)	Single-center, double-blind, randomized, controlled trial	TRT reduced fat mass at 12 months compared to placebo −1.35 kg, (95% CI: −2.53, −0.18).	Kreiberg *et al.* [82]
138 men with hypogonadal	Clinical trial (225 mg TU orally twice daily)	Small increase in ABP after 4 months of oral TU.	White *et al.* [83]
83 elderly men with obesity and hypogonadism	Randomized, double-blind, placebo-controlled trial (Randomized to lifestyle therapy (weight management and exercise training) plus testosterone (LT + Test) or placebo (LT + Pbo) for 6 months	Older, obese, low-dose men are unlikely to improve physical performance despite the addition of testosterone. However, muscle mass and hip BMD may improve.	Barnouin *et al.* [84]
5204 men	Randomized, placebo-controlled trial of daily 1.62% testosterone gel or placebo gel, stratified for preexisting CVD	In middle-aged and older men with anemia, TRT was found to be more effective than a placebo in correcting anemia. In men without anemia, the TRT treatment group had a lower rate of anemia.	Pencina *et al.* [85]

cFT: calculated free testosterone; TCS: testicular cancer survivors; TRT: testosterone replacement testosterone; CI: confidence Interval; LT: Lifestyle therapy; BMD: bone mineral density; CTX: c-terminal telopeptide of type I collagen; P1NP: n-terminal propeptide of type 1 procollagen; PCa: prostate cancer; CVD: cardiovascular disease; TU: testosterone undecanoate; ABP: ambulatory blood pressure; Pbo: placebo.

kinase (MAPKs) pathway activation in the testes [89].

Male oxidative stress infertility (MOSI), a term for male infertility from an oxidative stress (OS) perspective, is characterized by abnormal semen parameters and OS, and its treatment requires the use of the appropriate combination, dose, and duration of OS [90]. This approach discusses the pathophysiology of idiopathic male infertility (IMI) and how oxidation-reduction potential (ORP) can be used as a clinical biomarker of MOSI management. Oral anti-oxidant intake, stem cell, and next-generation sequencing (NGS) technologies can also help modulate male infertility [91, 92]. Antioxidants have been linked to male hormonal issues [93]. Studies have shown that taking antioxidant supplements can lead to DNA fragmentation in sperm cells [94]. This process damages or breaks the DNA strands, which in turn reduces the sperm's ability to fertilize an egg, ultimately resulting in decreased fertility. However, despite this negative effect, antioxidants have been found to play a crucial role in boosting male fertility [95]. Male erectile dysfunction (ED), ejaculation, and infertility all common issues [96]. Ejaculation can be treated with methods such as penile vibration stimulation, electroejaculation, and testicular sperm extraction. Hypothermia and anhedonia are common causes of poor sperm quality [97]. Taurine can help protect male fertility by reducing oxidative stress, increasing antioxidant capacity, inhibiting inflammation and apoptosis, restoring HPT axis secretory activity, reducing chromosomal alterations, improving sperm mitochondrial energy metabolism, and stabilizing cell membranes [98]. Natural products can improve testicular function, semen quality, and ROS scavenging [99]. When ROS production exceeds the body's antioxidant capacity, oxidative stress occurs, leading to cellular enzyme inactivation, germ cell death, and DNA damage. This ultimately reduces fertility [100–102]. However, our study has some limitations, as is the case with any

meta-analysis. The data we used is 24 years old, which may not reflect current trends. Additionally, our findings did not explore the relationship between treatment type and sperm quality, which can vary from person to person. Therefore, future research should assess the conditions and severity of sperm quality to draw more accurate conclusions. In this study, we focused on fertility treatments for men based on the relationship between male hormone-based fertility and male aging. While this is a significant advancement in improving aging in men, future research should also consider the risk of disease in specific male fertility treatment patients.

5. Conclusions

Testosterone levels not only affect male fertility but also affect a man's physical and mental health. Testosterone is known for its anti-inflammatory and antioxidant properties, especially in the synthesis of testosterone in Leydig cells. Decreased testosterone levels can lower semen quality and reduce fertility, so it is crucial to maintain a healthy lifestyle, exercise regularly, and opt for pharmacologic treatments that can maintain testosterone and increase serum levels. Although it is common for men to experience a decline in reproductive function and fertility as they age, declining testosterone levels are directly linked to health issues in men. Therefore, increasing testosterone levels to maintain healthy gonadal function can have a positive impact on a man's quality of life. Lately, there has been a trend towards the use of testosterone-based therapies for male fertility that utilize pharmacological treatments from natural sources. It can compensate for sperm quality issues and is associated with improved semen quality and ROS scavenging capacity, protecting against oxidative stress-induced DNA damage. As such, research into the development of new therapies based on natural products to improve male fertility should be pursued. It should be accompanied by a diversity of clinical trials that take into account genes and DNA damage. Thus, this review contends that germ cells have an organic relationship with a variety of aging effects and reduced fertility. This study is significant because it establishes the foundation for a fundamental mechanism underlying the link between male fertility and aging effects. However, the maintenance of healthy reproductive function in men has been dominated by studies investigating the underlying mechanisms of its action. New pharmacological evaluation studies should be conducted to focus on the main directions of medicinal research on male reproductive function and to fully realize the medicinal value of the plant based on natural product-based pharmacotherapy.

ABBREVIATIONS

ROS, reactive oxygen species; NADH, nicotinamide adenine dinucleotide; NADPH, nicotinamide adenine dinucleotide phosphate; P1NP, procollagen type 1 N-terminal propeptide; CI, confidence Interval; LT: Lifestyle therapy; NAD, nicotinamide adenine dinucleotide; LOH, late-onset hypoqonadism; NAD^+, nicotinamide adenine dinucleotide$^+$; ROS, reactive oxygen species; GSH, glutathione; TRT, testosterone replacement therapy; mtDNA, mitochondria DNA; SFA, saturate fats; PUFAs, polyunsaturated fatty acids; QOL, quality of life; LH, luteinizing hormone; GnRH, gonadotropin-releasing hormone; TNF-α, tumor necrosis factor-alpha; IL-6, interleukin-6; LHRH, luteinizing hormone-releasing hormone; p38 MAPK, p38 mitogen-activated protein kinase; EDC, endocrine disrupting chemical; p,p′-DDE, dichlorodiphenyldichloroethylene; FSH, follicle stimulating hormone; GnRH, Gonadotropin releasing hormones; HOS, hypo-osmotic swelling; StAR, steroidogenic acute regulatory protein; CVD, cardiovascular disease; LUTS, lower urinary tract symptoms; BMD, bone mineral density; PCa, prostate cancer; TU, testosterone undecanoate; AMP, ambulatory blood pressure; GSLS, ginseng stem-leaf saponins; MAPKs, mitogen-activated protein kinase; IMI, idiopathic male infertility; MOSI, Male oxidative stress infertility; ORP, oxidation-reduction potential; ED, erectile dysfunction; cFT, calculated free testosterone.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

YP and KHK—Conceptualization, vali-dation, writing-review. YP—methodology, software, formal analysis, investigation, resources, data curation, writing-original draft preparation, editing, visualization. KHK—supervision. All authors have read and agreed to the published version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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