



# The influence of anti-aging approaches on testosterone levels in sedentary elderly men

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## Abstract

**Introduction.** With thirty percent of the world's population not getting enough exercise, Worldwide, physical inactivity ranks as one of the most common cause of premature mortality. Rapid drops in physical activity, decreased mobility, and early morbidity are characteristics of aging. As the population over 80 continues to rise, aging raises the danger of age-related illnesses and changes in hormone release.

**Aim.** Understanding the aging process is useful in developing pharmacological therapies and identifying therapeutic targets for age-related testosterone deficiency. Therefore, the purpose of this study is to present a thorough evaluation of the effects of anti-aging strategies on testosterone levels in older, inactive men.

**Methods.** A literature search was completed for clinical and preclinical studies published in English between 2016 and 2024 related to age, sedentary life, testosterone, and anti-aging strategies.

**Results.** Age-related diseases can be prevented and treated by anti-aging techniques including calorie restriction, a balanced diet, regular exercise, weight control, diabetes management, and quitting smoking. Regular exercise raises total testosterone, free testosterone, and muscle steroidogenesis. In older men, testosterone replacement treatment increases bone density, cholesterol, protein synthesis, strength, erectile function, sexual desire, and general cognitive performance. Dehydroepiandrosterone supplementation, however, may improve health without having a detrimental impact, perhaps reversing arterial age and lowering the risk of cardiovascular disorders, according to certain research.

**Conclusion.** This article evaluates the prospects for anti-aging procedures to assist in reducing the adverse effects of aging and physical inactivity in men.

**Keywords:** sedentary life, testosterone, testosterone replacement therapy, elderly men.

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## Тестостерон при старении, связанном с сидячим образом жизни, и стратегии борьбы со старением

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## Аннотация

**Введение.** Поскольку 30% населения мира не получают достаточной физической нагрузки, отсутствие физической активности считается одной из наиболее распространенных причин преждевременной смертности во всем мире. Стремительное снижение физической активности, уменьшение подвижности и ранняя заболеваемость являются признаками старения. По мере того, как людей в возрасте старше 80 лет становится все больше, старение создает угрозу возрастных заболеваний и изменений процесса высвобождения гормонов.

**Цель.** Понимание процесса старения важно для разработки фармакотерапии и идентификации мишеней для лечения возрастного дефицита тестостерона. Таким образом, целью настоящей работы было представить полную оценку влияния стратегий борьбы со старением на уровень тестостерона у пожилых малоподвижных мужчин.

**Методы.** Выполнен поиск опубликованных с 2016 по 2024 г. англоязычных литературных источников о клинических и доклинических исследованиях, посвященных изучению возраста, сидячего образа жизни, тестостерона и стратегий борьбы со старением.

**Результаты.** Возрастные заболевания можно предупреждать и лечить, используя методы замедления старения, такие как сокращение калорийности рациона, сбалансированная диета, регулярные физические упражнения, контроль массы тела, контроль диабета и отказ от курения. Регулярные физические упражнения обеспечивают повышение уровня общего тестостерона, свободного тестостерона, стероидогенеза во время мышечной работы. У мужчин старшего возраста заместительная терапия тестостероном обеспечивает повышение плотности костной ткани, улучшает уровень холестерина, синтез белков, физическую силу, эректильную функцию, половое влечение и когнитивные способности. При этом биодобавки с дегидроэпиандростероном могут улучшать здоровье, не оказывая пагубного воздействия. По данным ряда исследований, они могут обратить вспять процесс старения сосудов и снизить риск сердечно-сосудистых заболеваний.

**Заключение.** В статье представлена оценка перспектив применения омолаживающих процедур для уменьшения неблагоприятных последствий старения и отсутствия физической активности у мужчин.

**Ключевые слова:** сидячий образ жизни, тестостерон, заместительная терапия тестостероном, пожилые мужчины.

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## Introduction

Worldwide, physical inactivity ranks as one of the most common cause of premature mortality (6% of deaths glob-

ally) [1]. According to World Health Organization's estimates, 31% of people worldwide do not engage in regular exercise to maintain their health [2]. According to data,

women are generally less active than males, and there are notable regional and national variations in physical activity levels. It is greatest in nations with high incomes. Owing to shifting mobility patterns, rising technological use, and urbanization, inactivity rates in some nations can reach 70% [3]. There is a negative correlation between physical inactivity and chronic illnesses, non-communicable diseases, and early death [4]. According to estimates, physical inactivity contributes between 6% and 10% of premature deaths worldwide, 30% of instances of coronary heart disease, 27% of type 2 diabetes, and obesity, and between 21% and 25% of cases of breast and colon cancer [5].

Aging is characterized by abrupt declines in physical activity, a reduction in mobility and functional independence, and an early onset of morbidity. The proportion of people 60 years of age and older is increasing. By 2030, there will be 1.4 billion people in the world who are 60 years of age or older, by 2050, that number will rise to 2.1 billion [6].

Aging increases the risks of many illnesses, such as diabetes, heart diseases, cataracts, arthritis, osteoporosis, benign prostatic hyperplasia, stroke, chronic obstructive pulmonary disease, cancer, and neurodegenerative diseases. Also, it is related to alterations in the secretion of certain hormones for example growth hormone, thyroid hormone, dehydroepiandrosterone, and insulin-like growth factor [7].

Elderly men are at risk of sedentary lifestyles. Since aging causes majority of chronic illnesses, understanding the aging process is expected to help discover therapeutic targets for age-related testosterone insufficiency and create pharmacological treatments appropriate for authorized clinical use in the future [8]. Therefore, this review aims to provide a systematic overview of the effect of antiaging strategies on testosterone in sedentary older males.

### The decline of testosterone with age

Testosterone levels in men begin to decline at around 30 to 40 years of age and continue until death [9]. Annually the level of testosterone decreases at a rate of around 2.8% [10]. Twenty percent of men in their 60s and over fifty percent of men in their 80s had serum testosterone levels considerably subnormal [9].

Local and systemic illness, prescription medications, lung tumors, excessive smoking or alcohol, obesity, and untreated diabetes were correlated with a decrease in testosterone [11]. Testosterone levels have been reported in untreated elderly diabetic males approximately 15% lower compared to their non-diabetic counterparts [12]. Opiates and anticonvulsants, can negatively impact testosterone production by altering hormonal signaling or enzyme activity. Opiates change the luteinizing hormone (LH) pulsatility while anticonvulsants decrease the hepatic enzyme induction [15]. Regardless of age, both smoking and lung tumors lower testosterone levels [16]. According to J. Okwara et al. [17], chronic alcohol users had testosterone levels that were 12% lower than those of non-drinkers. Low testosterone levels are strongly linked to male obesity and diabetes. Reduced levels of testosterone are closely associated with a number of variables, including visceral obesity, insulin re-

sistance, poor glycemic control, and longer duration of diabetes [18].

There are many factors involved in the reduction of testosterone levels with aging. These factors include a reduction in the pituitary LH and gonadotropin-releasing hormone releases and Leydig cell number and Leydig cell responsiveness (Leydig cell aging). Aging is associated with a dampening of the diurnal rhythm of testosterone secretion with a rise in the levels of sex hormone-binding globulins. This rise in sex hormone-binding globulin levels is caused by a rise in manufacture [19].

The reduction of testosterone level is associated with depression, fatigue, decreased energy level, deteriorated muscle and bone mass, difficulty concentrating, hot flashes, sexual dysfunction, such as impotence, erectile dysfunction, and decreased libido, sarcopenia, as well as a rise in mortality from heart disease, hypertension, dyslipidemia, obesity, diabetes, and insulin resistance [20].

### The decline of testosterone with an inactive lifestyle

Men's normal decrease in testosterone with age is greatly accelerated by a sedentary lifestyle. A sedentary lifestyle can significantly contribute to decline testosterone levels. The mechanisms of subnormal levels of testosterone include reduced blood flow, high body fat, loss of muscle mass, increase of stress, and disrupted sleep [21].

A decrease in blood flow leads to impairment of testosterone production [22]. Inactivity is associated with weight gain and an increase in body fat (specifically visceral fat) that can convert testosterone into estrogen, further lowering your hormone levels. Visceral fat secretes hormones and inflammatory agents. Chronic inflammation triggered by excess fat disrupts the signaling processes involved in testosterone synthesis, directly suppressing its production [21].

Without regular exercise, there is a loss of muscle mass. This can decrease testosterone production, as muscle mass plays a vital role in hormone synthesis [23]. Higher stress levels and disrupted sleep can disrupt hormone balance and lower testosterone. Cortisol, your primary stress hormone, directly antagonizes testosterone production. Deep sleep is necessary for the synthesis of the most testosterone [24].

Antiaging strategies. These strategies can encompass a range of lifestyle modifications, medical therapies and stem Leydig cell transplantation.

### Lifestyle modifications

They include physical activity, a balanced diet, and healthy sleep. It has been demonstrated that maintaining a normal weight and exercise level can safely raise testosterone secretion. A normal body weight reduces the risk of low testosterone levels associated with obesity [25].

### A. Physical activity

All physical activities, however, have the capacity to enhance well-being if they are performed regularly, for an adequate amount of time, and with sufficient intensity. In order to benefit from many of these advantages, the World

Health Organization's physical activity guidelines advise people to exercise for at least 150–300 minutes a week at a moderate to intense level or 75–150 minutes a week at a vigorous level, or an equivalent combination [26]. It could be necessary to engage in greater activity if one wants to maintain or lose weight [27].

Physical activity improves the following health outcomes: decreased anxiety and depressive symptoms, better sleep, increased mortality from cardiovascular disease and other causes, incident hypertension, incident cancers specific to specific sites, incident type-2 diabetes, and improved measures of adiposity. Engaging in physical activity assists elderly individuals in preventing falls, the harm they cause, and the decline in their bone density and functional capacity [26].

The most effective non-pharmacological method for raising testosterone production is regular exercise. The level of testosterone depends upon type (i.e., resistance or endurance), frequency, volume, intensity (high, moderate, and low), and duration of exercise [1]. Acute endurance exercise (such as running, cycling, or swimming) increases the testosterone level while chronic high-volume endurance exercise may lead to lower testosterone levels. Strength training or weightlifting is generally associated with increases in testosterone levels. Compound movements (like squats or deadlifts) that engage multiple muscle groups are particularly effective. Regular, consistent training (as opposed to sporadic sessions) tends to lead to better hormonal responses [26]. However, overtraining or inadequate recovery can suppress testosterone levels. The amount of muscle involved in resistance exercises affects testosterone response. Larger muscle groups (e.g., legs and back) tend to elicit a greater hormonal response than smaller muscle groups. Higher volume (more sets and repetitions) often results in greater acute increases in testosterone [27]. Increases in testosterone are often observed after high-intensity resistance training sessions. Short-duration, high-intensity workouts typically lead to acute increases in testosterone. However, prolonged exercise (especially at high volumes in endurance sports) can result in a decrease in testosterone levels due to increased cortisol production and energy deficit [22].

## B. Sleep

Prioritizing sleep is essential for physical and mental restoration. Chronic sleep deprivation can accelerate aging and is associated with decline testosterone levels. The symptoms of testosterone insufficiency and self-reported sleep quality are correlated linearly [28].

## C. Stress management

Chronic stress is likely to lower your testosterone levels due to the direct inhibition of cortisol on Leydig cells and the hypothalamic-pituitary-gonadal axis. Reducing stress through techniques like mindfulness, yoga, or meditation can lower cortisol levels and elevate testosterone levels [29].

## D. Nutrition

Consuming a balanced diet composed of an abundance of healthful grains, fruits, veggies, lean meats, and healthy fats

can help supply essential nutrients essential for testosterone production and combat oxidative stress and inflammation [24]. Total testosterone levels significantly increased in response to a weight-loss diet, both with and without frequent exercise [28]. When honey is taken orally, it raises men's blood testosterone levels via stimulating the synthesis of LH. It is packed with antioxidants, minerals (such as zinc), and many vitamins (including B vitamins). Particularly zinc is recognized to be essential for the synthesis of testosterone [29].

## Caloric restriction

Caloric restriction (CR) is the reducing caloric intake by 20–60% without malnutrition. It delays age-related disorders and can increase the lifespan of mice by as much as 40% or more. Its effects on testosterone levels by different factors, such as the degree of CR, the duration of the diet, the individual's age, sex, and overall health status. Some studies suggest that short-term CR can lead to a decline in testosterone levels. This is because the body's adaptive response to reduced energy availability, where it conserves energy and minimizes reproductive functions, including testosterone production [30].

Long-term calorie restriction frequently results in weight loss, and in overweight or obese people in particular, a decrease in body fat may have a favorable impact on testosterone levels. Excess visceral fat is associated with lower testosterone levels, so losing fat can help restore or improve hormonal balance. This happens through two different mechanisms: enhanced testicular function and decreased testosterone conversion to  $\beta$ -estradiol via adipose tissue's aromatase activity [31].

## CR mimetics

CR mimetics are compounds that aim to mimic the physiological effects of calorie restriction without actually reducing caloric intake. The CR mimetics include natural compounds (such as resveratrol, curcumin, and quercetin), and pharmacological drugs (such as metformin and rapamycin) [32].

A significant natural polyphenolic chemical, resveratrol may be found in several fruits and vegetables, including peanuts, grapes, and peanut sprouts. It is a sirtuin-activating compound that has been shown to extend lifespan and modulate insulin secretion and action [33]. Resveratrol effectively inhibits a number of processes, including angiogenesis, oxidative stress, apoptosis, inflammation, and mitochondrial malfunction. Furthermore, it inhibits platelet aggregation to further exhibit its cardioprotective effects [34]. It has been demonstrated that resveratrol supplementation causes a penile erection, reduces germ cell apoptosis, increases blood testosterone concentration, and enhances sperm quality and epididymal sperm count [35]. The hypothalamic-pituitary-gonadal axis is directly stimulated by resveratrol while, the testes are unaffected [36].

Curcumin, derived from turmeric, curcumin has antioxidant, anti-inflammatory, and antiapoptotic properties. It enhanced testicular hemodynamics, follicle-stimulating

hormone, testosterone, and nitric oxide levels while markedly suppressing the lipid profile [37].

Quercetin, present in vegetables and fruits may mimic some effects of CR and promote health span [38]. It has been shown that quercetin inhibits the enzyme that converts testosterone into testosterone glucuronide, enhancing testicular functioning and testosterone levels [39].

### Medical therapies

Testosterone replacement therapy in old man led to advancements in physical function, strength, protein synthesis, cholesterol, and bone density. It may increase total sexual satisfaction, strengthen erectile function, and increase sexual desire. It is widely recognized to support erythropoiesis, mood, muscle mass, bone density, body composition, and cognitive performance, including working memory, verbal, spatial, and visual. Administering testosterone elevates the expression of genes and glucose transporter type 4 and enhances the activity of glycolytic enzymes (hexokinase, phosphofruktokinase, and glycogen synthase) [40].

However, not every elderly man will benefit from this replacement. According to some studies, testosterone replacement therapy for older men does not significantly improve strength or cognitive function, but it does cause coronary artery plaque to build and is consistently found to have no effect on insulin sensitivity. Regular monitoring of testosterone levels, as well as screenings for prostate health and blood counts, is crucial during replacement [41]. While the effectiveness of testosterone replacement therapy is still debatable, some have hypothesized that administering the testosterone precursor dehydroepiandrosterone might enhance health without having adverse consequences [42].

Male hypogonadism can be effectively treated using gonadotropins, such as human chorionic gonadotropin (approved by U.S. Food and Drug Administration for this purpose). However, gonadotropins are expensive and must be administered by intramuscular or subcutaneous injection. Human chorionic gonadotropin has the same structure and function as the LH [27]. It is both safer and more efficient treatment and can be used in patients with pituitary dysfunction. It stimulates the testes to produce more testosterone and is particularly useful for men desiring to preserve spermatogenesis and fertility [43].

Long-term usage of selective estrogen receptor modulators, seems to be safe and well-tolerated, and it appears to be quite successful at generating physiologic testosterone levels. Selective estrogen receptor modulators enhance the

synthesis of LH and subsequent testosterone by blocking the negative feedback that estrogen has on the hypothalamus. It is used to restore testosterone levels while preserving fertility by stimulating the body's testosterone production [44].

Aromatase inhibitors can help increase testosterone levels by preventing the conversion of testosterone to estrogen, thus enhancing endogenous testosterone production. These drugs may also increase testosterone levels, but if used over an extended period of time, the suppression of estrogen may result in decreased bone mineral density. They are also designed to prevent the tissues from converting testosterone into estrogen, which suppresses the hypothalamic-pituitary-gonadal axis in the presence of estrogen [45].

It also was found that nerve growth factor increased LH, follicle-stimulating hormone, and testosterone levels as well as indices of sexual behavior in mice, such as mounting and ejaculation times [46].

It has also been demonstrated that oxytocin stimulates the production of gonadotropin-releasing hormone, and it has been suggested that intranasal oxytocin might one day be used as a treatment for testosterone insufficiency [47].

Senolytics, including dasatinib, fisetin, and navitoclax, improved sperm concentration and serum testosterone levels while decreasing aberrant sperm morphology; they had no effect on fertility. The antioxidant impact is what causes this result [48].

Osteoporosis, diminished cognitive function, loss of muscular mass and function, and a notable reduction of rat testis and spermatogenesis are all linked to vitamin D insufficiency in the elderly [49]. Reduced androgen production is at least partially responsible for these findings [50].

### Stem Leydig cell transplantation

It can undergo differentiation into fully developed Leydig cells, be subject to hypothalamic-pituitary-gonadal axis regulation, and reestablish circadian rhythm testosterone production. Most of the current research on stem Leydig cell transplantation has been conducted in animal models [51]. More research is needed to translate these findings into clinical applications for humans. Factors such as the source of stem cells, transplantation techniques, and the long-term effects of such interventions are still under investigation.

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