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The Action of Testosterone in Anti-aging, Rejuvenation, and Longevity

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Abstract: Testosterone is an anabolic androgenic steroid hormone, that is, it is a lipid synthesized from cholesterol-steroid, produced by glands and with regulatory action on cellular physiology hormone, whose main actions are to promote masculinization -androgenic effect- and the synthesis of complex molecules from simpler molecules anabolic effect. Our body's three main steroid substances are androgens, estrogens, and corticosteroids. This literature review aims to verify testosterone's action on rejuvenation, anti-aging, and longevity. The integrative literature review is a method that aims to synthesize results obtained in research on a topic or issue, in a systematic, ordered, and comprehensive way. It is called integrative because it provides broader information on a subject/problem, thus constituting a body of knowledge. To carry out the study, a search for scientific articles was carried out through the Virtual Health Library (SCIELO), Latin American and Caribbean Literature in Health Sciences (LILACS), US National Library of Medicine National Center for Biotechnology Information (PUBMED), Social Network for Scientists (ResearchGate) and Virtual Social Network for Academics (Academia.edu) using the terminologies registered in the health sciences descriptors: Anti-aging, hormones, longevity, rejuvenation, and testosterone.

Keywords: Aging, Biosynthesis, Hormones, Regulation, Replacement.

Review Paper

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1. INTRODUCTION

Population aging is set to become one of the most significant social transformations of the 21st century, with implications for all sectors of society in the labor and financial markets; in the demand for goods and services such as housing, transport, and social protection; and family structures and intergenerational ties. The number of older people, aged 60 and over, is expected to double by 2050 and more than triple by 2100, from 962 million in 2017 to 2.1 billion in 2050 and 3.1 billion in 2100. Across the world, the population aged 60 and over is growing faster than all younger age groups. The population over 60 is growing at a rate of around 3% per year. In 2017, an estimated 962 million people worldwide were aged 60 or over representing 13% of the global population (United Nations, 2024).

Europe currently has the highest percentage of the population aged 60 or over (25%). Rapid aging will also occur in other parts of the world, and by 2050, all regions except Africa will have almost a quarter or more of their populations aged over 60. Globally, the number of people aged 80 or over is expected to triple by 2050, from 137 million in 2017 to 425 million in 2050 (Information for Western Europe, 2024; United Nations, 2024).

Older people are increasingly seen as contributors to development, whose capabilities must be interconnected with cross-cutting policies and programs. However, in the coming decades, many countries will face fiscal and political pressures on public health, welfare, and social protection systems for older people (Information for Western Europe, 2024; United Nations, 2024).

While declining fertility and increasing longevity are the main drivers of population aging worldwide, international migration has also contributed to changing population age structures in some countries and regions. In countries experiencing large immigration flows, international migration can slow the aging process, at least temporarily, as migrants tend to be young (Information for Western Europe, 2024; United Nations, 2024).

1.1 Testosterone

Testosterone is an anabolic androgenic steroid hormone, that is, it is a lipid synthesized from

cholesterol-steroid, produced by glands and with regulatory action on cellular physiology hormone, whose main actions are to promote masculinization -androgenic effect- and the synthesis of complex molecules from simpler molecules anabolic effect. Our body's three main steroid substances are androgens, estrogens, and corticosteroids Comb. Enthalpy: 11080 kJ/mol. Excretion: Urine. Molecular formula: $C_{19}H_{28}O_2$, Molar mass: 288.43. Half-life: 1-12 days) (Figure 1) (Torjesen and Sandnes, 2004; Tuck and Francis, 2009; Raggatt and Partridge, 2010).

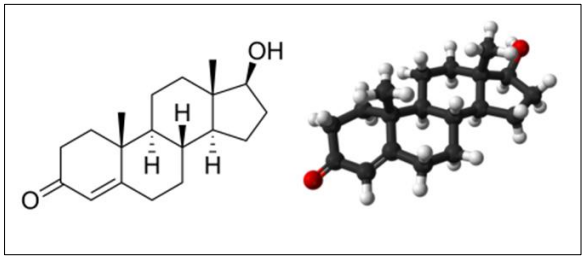

Figure 1: Testosterone is the most important androgen in humans, and regulates libido, energy, immune function, muscle development, and bone health
Source: https://pt.wikipedia.org/wiki/Testosterona

Androgens, the main representative of which is testosterone, are responsible for the development of masculine characteristics. Estrogens are the hormones responsible for the development of feminine traits. Corticosteroids are accountable for a wide variety of essential bodily functions, involving the immune, cardiovascular, metabolic, and various metabolic activities, such as the production of blood cells in the bone marrow, lipid metabolism, bone formation, carbohydrate metabolism, prostate growth, and liver function. and hemostatic systems (Figure 2) (Torjesen and Sandnes, 2004; Tuck and Francis, 2009; Raggatt and Partridge, 2010; Luetjens and Weinbauer, 2012; Kelsey *et al.*, 2014; Favaretto, 2024; Pinheiro, 2024).

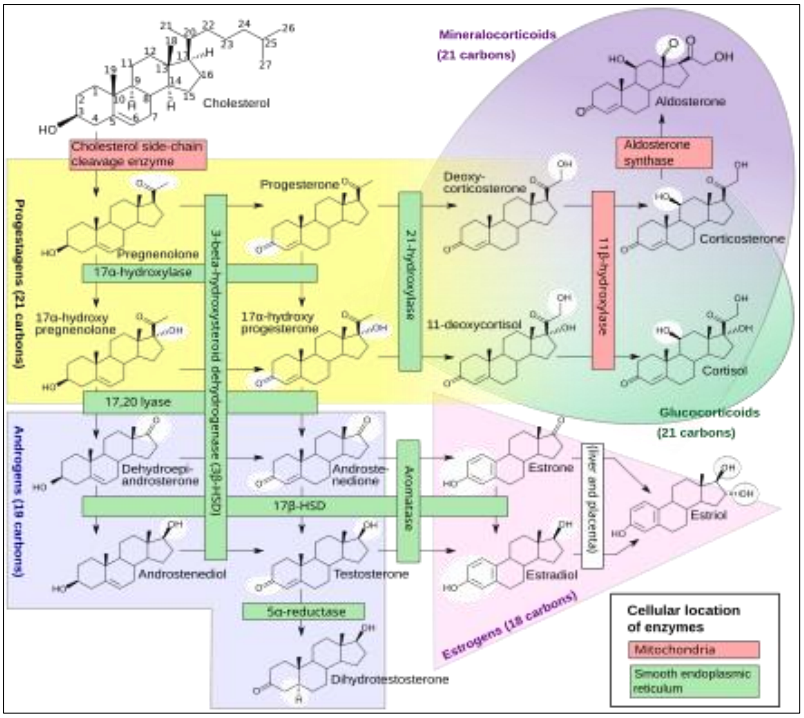

Figure 2: Like other steroid hormones, testosterone is derived from cholesterol. The first step in biosynthesis involves the oxidative cleavage of the cholesterol side chain by the cholesterol side-chain cleavage enzyme (P450scc, CYP11A1), a mitochondrial cytochrome P450 oxidase with the loss of six carbon atoms to give pregnenolone. In the next step, two additional carbon atoms are removed by the enzyme CYP17A1 (17alpha-hydroxylase/17,20-lyase) in the endoplasmic reticulum to produce a variety of C19 steroids. In addition, the 3β-hydroxyl group is oxidized by 3β-hydroxysteroid dehydrogenase to produce androstenedione. In the final and rate-limiting step, the C17 androstenedione keto group is reduced by 17β-hydroxysteroid dehydrogenase to produce testosterone

Source: https://www.precisionnutrition.com/all-about-testosterone, Doi:10.1159/000182546 and Doi:10.1126/science.3535074

Testosterone is a steroid. It is synthesized in several steps from cholesterol and is converted in the liver to inactive metabolites. It exerts its action through binding to and activation of the androgen receptor. In humans and most other vertebrates, testosterone is secreted primarily by the testes of males and, to a lesser extent, by the ovaries of females. Women produce a large amount of estrogen in the ovaries and a small amount of testosterone in the adrenal gland and ovaries. Men produce a large amount of testosterone in their testicles and a small amount of estrogen in their liver, adipose tissue, and brain. Testosterone production by the testicles is stimulated by LH (Luteinizing Hormone), a hormone produced by the pituitary gland in the brain. Whenever the pituitary gland increases the release of LH, the testicles respond by increasing testosterone production (Figure 3) (Plant and Marshall, 2001; Torjesen and Sandnes, 2004; Tuck and Francis, 2009; Raggatt and Partridge, 2010; Luetjens and Weinbauer, 2012; Stocco *et al.*, 2012; Marchetti and Barth, 2013; Choi and Smitz, 2014; Kelsey *et al.*, 2014; Schuster *et al.*, 2016; Grinspon *et al.* 2018; Favaretto, 2024; Pinheiro, 2024).

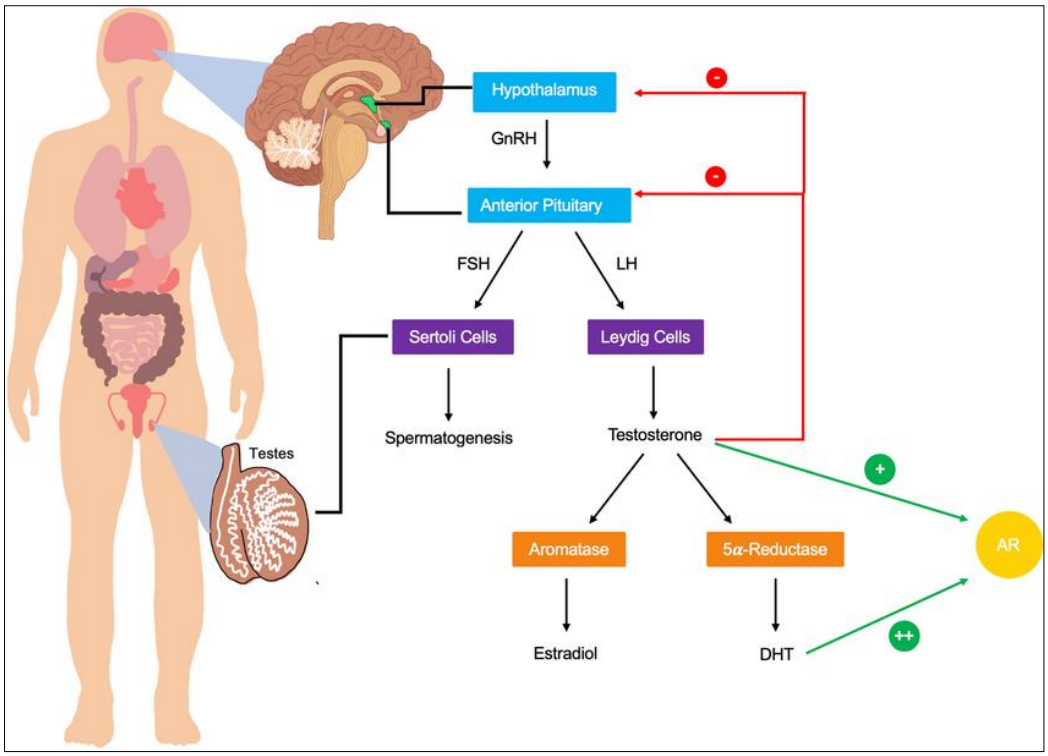

Figure 3: Regulation and metabolism of testosterone. Testosterone production begins in the hypothalamus when GnRH is released into the hypophyseal portal system and acts upon the anterior pituitary causing the release of FSH and LH. FSH acts on the Sertoli cells of the testes to stimulate spermatogenesis. LH acts on the testes' Leydig cells, causing the release of Testosterone. Testosterone is metabolized into DHT by the action of 5α-reductase. Both testosterone and DHT act on the AR with DHT exerting more potent effects. Aromatase converts testosterone into estradiol which regulates many bodily processes

Sources: https://www.researchgate.net/figure/Regulation-and-metabolism-of-testosterone-Testosterone-production-begins-in-the_fig1_366850889, Doi: 10.17925/EE.2018.14.2.67, Doi: 10.1210/edrv.22.6.0446, Doi: 10.1016/j.mce.2013.12.009, Doi: 10.1258/acb.2012.012159, Doi: 10.3758/s13415-012-0117-7 and Doi: 10.18632/oncotarget.4027

In men, testosterone production peaks at three distinct stages of life. The first peak occurs during the fetal period, in the second trimester of pregnancy, and is intended to develop the fetus with masculine physical characteristics. Later, during the first year of a boy's life, testosterone levels rise again, but no clear physical effect on the baby's body is perceived. It is believed that this peak serves to "masculinize" the brains of boys, shaping certain behaviors that are characteristic of the male sex. The third peak, which is the most obvious of all, occurs during puberty, resulting in several visible changes, such as voice change, increased body hair, genital maturation, sperm production by the testicles, thicker and oilier skin, increased libido, bone growth, increased muscle mass,

and reduced body fat (Figure 4) (Zuber *et al.*, 1986; Waterman and Keeney, 1992; Torjesen and Sandnes, 2004; Tuck and Francis, 2009; Raggatt and Partridge, 2010; Luetjens and Weinbauer, 2012; Kelsey *et al.*, 2014; Gryzinski and Bernie, 2022; Forciea *et al.*, 2023; Favaretto, 2024; Pinheiro, 2024).

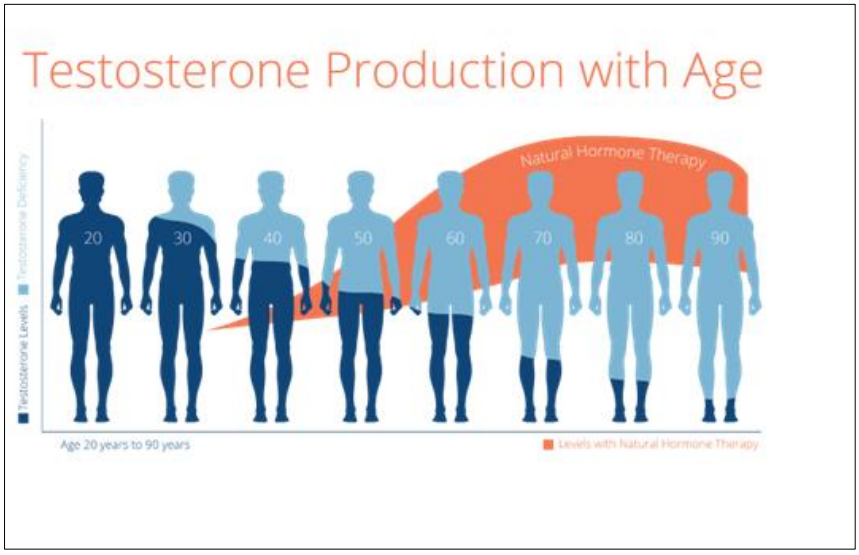

Figure 4: This is an answer that will vary for everybody; there is not a magic number that indicates normal testosterone levels for every person, although healthy testosterone levels tend to range from about 270 to 1,070 nanograms per deciliter (ng/dL). If there is an ideal level of testosterone, it would probably be the amount of testosterone in our bodies before we hit the age of 30. For most of us, our bodies produce increased amounts of testosterone throughout our adolescence and into our early adult years. Once most of us hit 30, testosterone can begin to decrease by as much as 1 percent each year, and that decrease can harm both men and women. After 40, that decrease becomes even more pronounced

Sources: https://annals.org/aim/fullarticle/2758507/testoterone-tratment-adult-men-age-related-low-testoterone-clinical-guideline and Doi: 10.7326/L23-0043

1.1. OBJECTIVES

This literature review aims to verify testosterone's action on rejuvenation, anti-aging, and longevity.

2.0 METHODS

The methodology used an integrative literature review and a synthesis process to develop the study to expand the understanding of knowledge and achieve the expected results. The integrative literature review is a method that aims to synthesize results obtained in research on a topic or issue, in a systematic, ordered, and comprehensive way. It is called integrative because it provides broader information on a subject/problem, thus constituting a body of knowledge. To carry out the study, a search for scientific articles was carried out through the Virtual Health Library (SCIELO), Latin American and Caribbean Literature in Health Sciences (LILACS), US National Library of Medicine National Center for Biotechnology Information (PUBMED), Social Network for Scientists (ResearchGate) and Virtual Social Network for Academics (Academia.edu) using the terminologies registered in the health sciences descriptors: Anti-aging, hormones, longevity, rejuvenation, and testosterone.

3.0. SELECTED STUDIES

3.1. Changes in the Body with Aging

Old cells sometimes die because they are programmed to do so. The genes in the cell program a process that, when triggered, results in the cell's death. This programmed death, called apoptosis, is a type of cellular suicide. The aging of a cell is one trigger. Old cells must die to make way for new cells. Other triggers include an excess of cells and possible damage to a cell. Old cells also die because they can only divide a limited number of times. This limit is programmed by the genes. When a cell can no longer divide, it grows, lives for a while, and then dies. The mechanism that limits cell division involves a structure called telomere (Figure 5) (Merck & Co., Inc., 2024; Stefanacci, 2024a; Stefanacci, 2024b; Stefanacci, 2024c).

The first signs of aging involve the musculoskeletal system. The eyes, followed by the ears, begin to change in early middle age. Most internal functions also decline with aging. Most bodily functions peak shortly before age 30 and begin a gradual but steady decline. However, even with this decline, most functions remain adequate because the functional capacity of almost all organs is greater than the body's requirements. If half of the liver is destroyed, the remaining liver tissue

is sufficient to maintain normal function. Disorders, rather than normal aging, account for most of the loss of functional capacity in old age (Palmer and Jensen, 2022; Merck & Co., Inc., 2024; Stefanacci, 2024a; Stefanacci, 2024b; Stefanacci, 2024c).

Telomeres are used to move the cell's genetic material in preparation for cell division. Each time the cell divides, the telomeres shorten a little. Eventually, the telomeres become so short that the cell can no longer divide. When a cell stops dividing, it is called senescence. Sometimes, damage to a cell directly causes its death. Cells can be damaged by harmful substances, such as radiation, sunlight, and chemotherapy drugs. Cells can also be damaged by certain byproducts of their normal activities. These byproducts, called free radicals, are released when cells produce energy (Figures 5, 6 and 7) (Almeida *et al.*, 2017; Merck & Co., Inc., 2024; Stefanacci, 2024a; Stefanacci, 2024b; Stefanacci, 2024c).

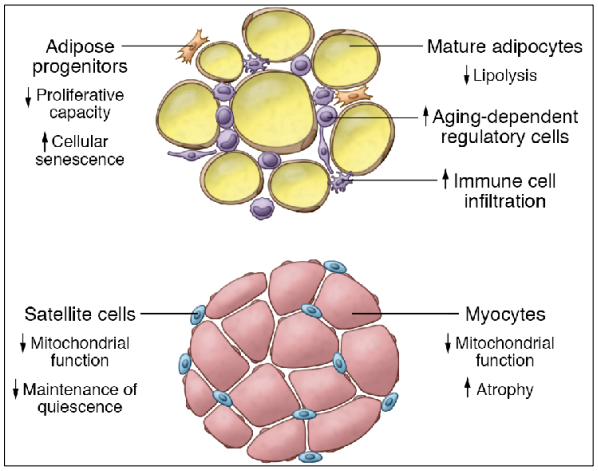

Figure 5: Cellular changes in adipose and skeletal muscle with aging. In adipose tissue, aged progenitor cells have reduced proliferative capacity and undergo more cellular senescence, and adipocytes' ability to undergo lipolysis is diminished. Immune cell infiltration increases with age, and accumulation of aging-dependent regulatory cells is seen. In skeletal muscle, mitochondrial function is decreased with aging, satellite cells lose the ability to maintain quiescence, and myocytes undergo atrophy

Source: https://www.researchgate.net/figure/Cellular-changes-in-adipose-and-skeletal-muscle-with-aging-In-adipose-tissue-aged_fig2_362699770

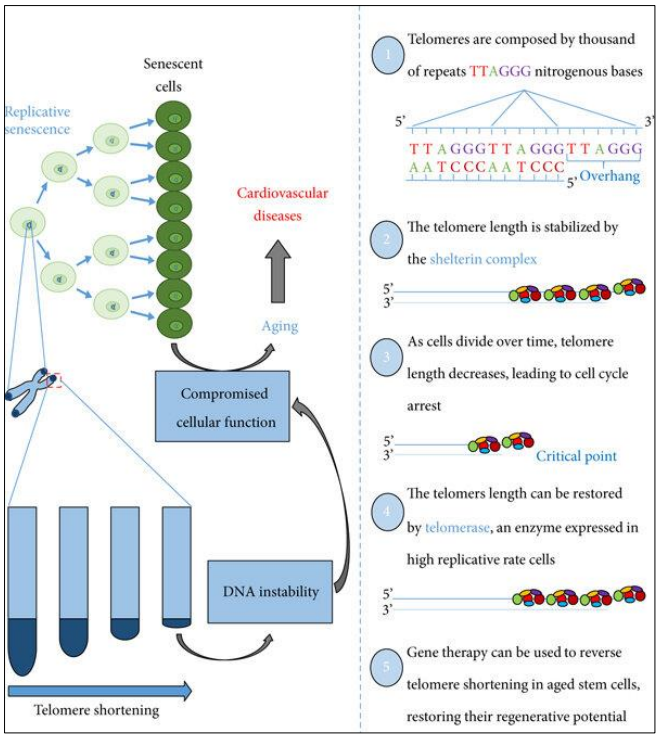

Figure 6: Role and function of telomeres in DNA protection. After each cell division, each chromosome loses a part of its telomeres, a region characterized by thousands of repeated sequences of nitrogenous bases. At a critical point, cells with shortened telomeres stop to divide, leading to senescence and resulting in aging and CVDs. Cells with high replicative rates such as stem cell lineages express telomerase, an enzyme capable of reversing telomere shortening. This enzyme plays a key role in the development of new therapies that aim to slow or reverse the aging process

Sources: https://www.researchgate.net/figure/Role-and-function-of-telomeres-in-DNA-protection-After-each-cell-division-each_fig5_319028311 and Doi: https://doi.org/10.1155/2017/7941563

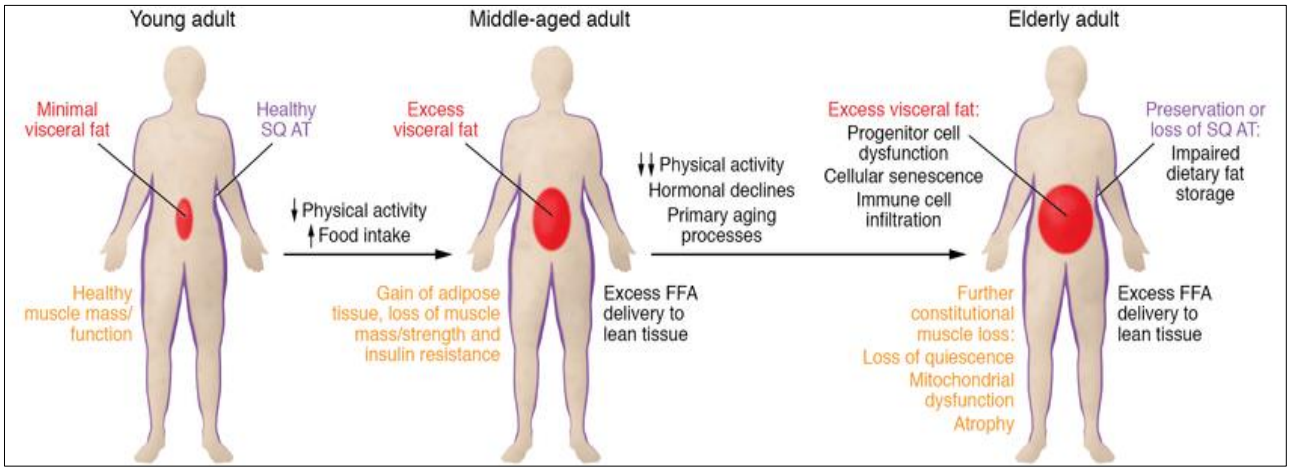

Figure 7: Body composition and metabolic changes with aging. The transition from healthy, active young adulthood (left), with healthy amounts and function of adipose tissue/muscle, through a sedentary lifestyle and weight gain shift to middle age (middle) to more extreme old age (right) is depicted. With a sedentary lifestyle and plentiful food, adults accumulate excess visceral fat, develop adipocyte hypertrophy in subcutaneous fat, and lose muscle mass and strength. Increased adipocyte size is associated with excess release of free fatty acids (FFAs), which have been shown to cause insulin resistance and other metabolic abnormalities; excess visceral fat causes excess FFA delivery to the liver. With extreme old age comes reduced anabolic hormones, and these reductions combined with the direct effects of aging and further declines in activity result in more muscle atrophy and greater adipose tissue dysfunction. There are primary aging mechanisms at both the cellular and the organism level. SQ AT, subcutaneous adipose tissue

Sources: https://www.researchgate.net/figure/Body-composition-and-metabolic-changes-with-aging-The-transition-from-healthy-active_fig1_362699770 and Doi: org/10.1172/JCI158451.

To achieve healthy aging, with autonomy and independence, it is essential to seek practices and care that favor improving quality of life and reducing the risks of illness. The consumption of healthy foods, the practice of daily physical exercises, and mental exercises that ward off sadness and depression, and avoiding alcoholic beverages, as well as tobacco. Testosterone replacement, for example, helps replace lean mass and improve muscle functions, substantially improving the strength and quality of life of the elderly, especially those living with sarcopenia. Thus, the present study aims to understand the impact of testosterone on the longevity of the elderly (Pessanha *et al.*, 2016; Thiago ad Camargo Júnior, 2016; Silva *et al.*, 2020; Santos *et al*., 2021).

To maintain body synthesis, the body needs the modulation of essential hormones, such as testosterone. This hormone has a significant impact on the structure and essential functions of skeletal muscles, in addition to directly influencing the process of muscle hypertrophy and strength. To improve performance, performing exercises associated with neuronal coordination can favor increases in muscle cross-sectional areas, thus favoring their development (Pacobahyba *et al.*, 2012; Silva *et al.*, 2020; Santos *et al.*, 2021).

Testosterone has its effect already identified and recognized, with its reduction impacting the emergence of sarcopenia and dynapenia. Low testosterone levels are common in older men and are associated with adverse outcomes such as diabetes, obesity, cardiovascular events, sarcopenia, osteoporosis, and decreased libido. Men with low testosterone levels increase mortality with an approximate doubling of the mortality risk compared to men with normal testosterone levels (Pícoli *et al.*, 2012; Tiggemann, 2013; Silva *et al.*, 2020; Santos *et al.*, 2021).

Sarcopenia is a musculoskeletal disease in which there is a reduction in muscle strength, performance, and mass, causing symptoms such as muscle weakness, loss of balance, and the inability to perform physical activities such as walking, climbing stairs, or getting out of bed. Sarcopenia is more common

after the age of 50, the period in which there is a greater reduction in the quantity and size of the fibers that form the muscles, a decrease in the production of hormones such as estrogen and testosterone in the body, in addition to a reduction in the practice of physical activity (Figure 8) (Rohden, 2011; Silva *et al.*, 2020; Villacorta, 2023; Bezerra, 2024).

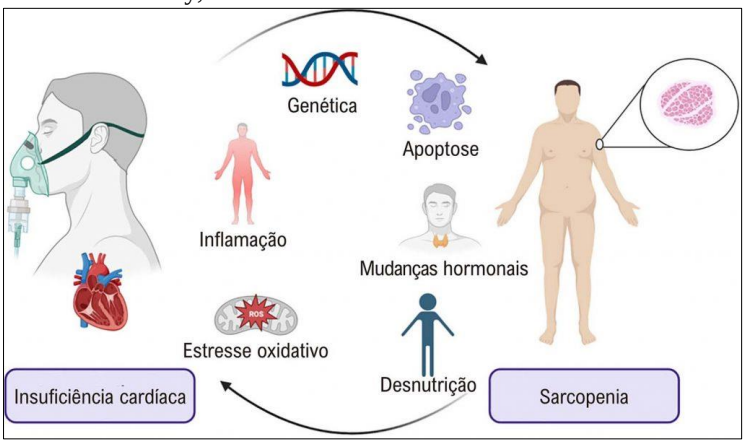

Figure 8: Heart failure and sarcopenia share some risk factors. Patients with heart failure may develop sarcopenia through the mechanisms outlined above, and sarcopenia indicates a worse prognosis in patients with heart failure

Source: Doi: 10.36660/abc.20230689

The main symptoms of sarcopenia are muscle weakness, loss of balance, increased risk of falls and fractures, loss of resistance, and decreased muscle size. One of the treatments for sarcopenia is hormone replacement therapy or testosterone. Studies have shown that testosterone replacement therapy in elderly sarcopenic patients significantly increases muscle tissue production and reduces adipogenesis. They concluded that testosterone administration can reduce the initial adipocyte percentage by 6.2% and increase lean mass by 1.6% (Thiago and Camargo Júnior, 2016; Silva *et al.*, 2020; Santos *et al.*, 2021; Bezerra, 2024).

The term dynapenia is used to define the loss of muscle strength and power related to aging, which is not caused by neurological or muscular diseases. Several studies have associated dynapenia with an increased risk of physical disability, poor physical performance, and even mortality. Thus, the preservation of muscle strength and power with advancing age is clinically relevant. However, research has suggested that other physiological factors, independent of the size of the muscle tissue, play a fundamental role in determining muscle weakness. This has made it clear that the force generated by a muscle is not directly proportional to the amount of muscle fiber present in it (Figure 9) (Clark and Manini, 2008; Castro, 2012; Clark and Manini, 2012a; Clark and Manini, 2012b).

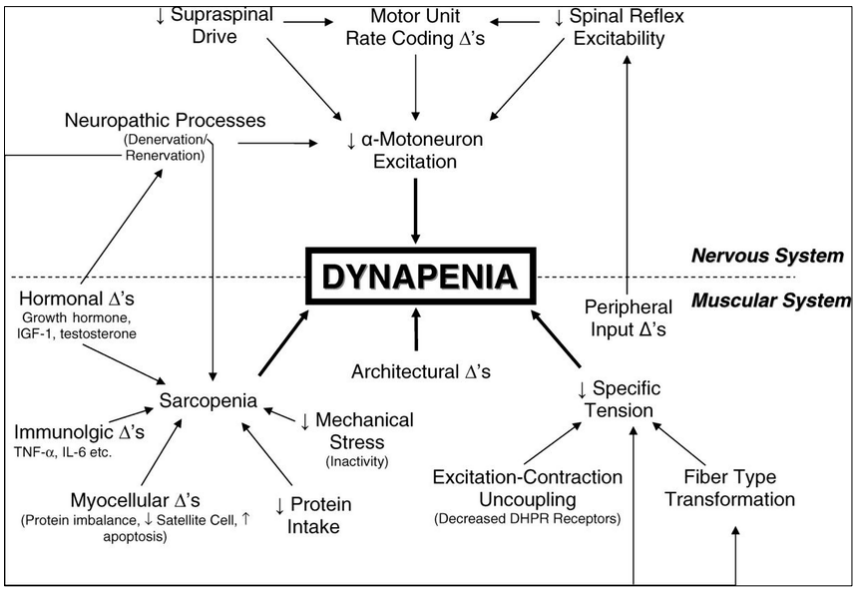

Figure 9: Etiology of sarcopenia and dynapenia. Figure summarizes the influence of multiple factors that may lead to aging-associated loss of muscle mass and dynapenia. IGF-1 = insulin-like growth factor 1; DHPR = dihydropyridine receptors; TNF-α = tumor necrosis factor-α; IL-6 = interleukin 6 [Doi: 10.1093/gerona/63.8.829]
Source: https://www.researchgate.net/figure/Etiology-of-sarcopenia-and-dynapenia-Figure-summarizes-the-influence-of-multiple-factors_fig1_264673459 and Doi: 10.1093/gerona/63.8.829

Testosterone improves bone mineral density in the head, femur, and lumbar spine, causes a drop in lipid profile markers such as HDL and total cholesterol, and is also capable of improving cardiac output and reducing peripheral vascular resistance, demonstrating an improvement in the quality of life of patients with this cardiac limitation. Its use in the elderly promotes improvements in changes related to erectile dysfunction, depression, anxiety, and loss of energy and, in andropause, increases longevity and psychological and emotional health (Rohden, 2011; Thiago ad Camargo Júnior, 2016; Silva *et al.*, 2020; Santos *et al.*, 2021; Bezerra, 2024).

The average serum concentration of total testosterone in young adults is approximately 650 ng/dL. Therefore, hormone replacement therapy is indicated when the presence of symptoms suggestive of androgen deficiency is associated with serum testosterone levels below 300 ng/dL and free testosterone levels below 6.5 ng/dL. Hormone replacement therapy in elderly men is a complex and constantly evolving topic. Based on the literature review, it is possible to infer that hormone replacement therapy can bring significant benefits to the quality of life of these individuals. Studies suggest that hormone replacement therapy can improve muscle mass, sexual function, and bone density, and reduce symptoms associated with hormone deficiency (Bonaccorsi, 2001; Borst and Mulligan, 2007; Casulari and Motan, 2008; Nigro and Christ-Crain, 2012; Rodrigues Filho, 2014).

3.3. Testosterone Rejuvenation Action

Testosterone levels decline as a process of aging: signs and symptoms caused by this decline can be considered normal as part of this process. However, low testosterone levels are also associated with severe chronic diseases and symptomatic patients may benefit from testosterone replacement therapy. However, it is essential to consider the risks and concerns related to hormone replacement therapy. Concerns such as potential increased cardiovascular risk, sleep disorders, prostate changes, and development of cancer need to be addressed carefully. Individualized clinical evaluation, adequate monitoring, and frank and open communication between physician and patient are essential for informed decision-making (Figure 10) (Moss *et al.*, 2013; Racaru-Honciuc *et al.*, 2014; Diamanti-Kandarakiset *et al.*, 2017; Handelsman, 2017; Rosenthal *et al.*, 2020; Matthew *et al.*, 2021; Wang *et al.*, 2021; Tramontano, 2023; Pontes Neto, 2024; Duet *et al.*, 2024).

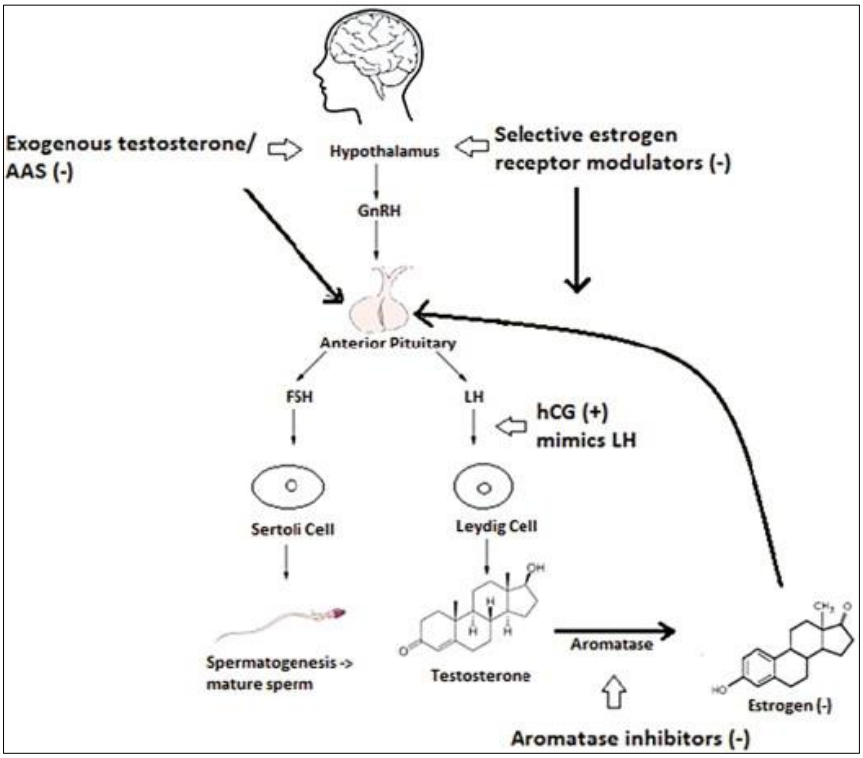

Figure 10: Rejuvenation hormones and mechanism of action. Exogenous testosterone and anabolic androgenic steroids (AAS) negatively affect the hypothalamic-pituitary-gonadal (HPG) axis. Selective estrogen receptor modulators (SERMs)block the negative feedback of estrogen on the HP Gaxis. Human chorionic gonadotropin (hCG)stimulates Leydig cells. Aromatase inhibitors prevent the conversion of testosterone to estrogen
Sources: Moss. Rejuvenation hormones and spermatogenesis. Doi.org/10.1016/j.fertnstert.2013.04.003

Furthermore, it is important to emphasize the need for high-quality studies, with representative samples and following rigorous protocols, to elucidate further the benefits and risks of hormone replacement therapy in elderly men. Such research should seek a deeper understanding of the mechanisms of action, the appropriate treatment time, the ideal doses, and the identification of subgroups of patients who may benefit differently (Bonaccorsi, 2001; Borst and Mulligan, 2007; Casulari and Motan, 2008; Nigro and Christ-Crain, 2012; Rodrigues Filho, 2014).

3.4. Testosterone Replacement Therapy (TRT)

The levels of some hormones decrease with age. Thus, people can try to slow or reduce aging by taking supplements of these hormones. Examples are testosterone, estrogen, DHEA (dehydroepiandrosterone), human growth hormone, and melatonin. However, there is no evidence that hormone supplements affect aging; some have known risks. Some experts even believe that reducing certain hormone levels may prolong life by reducing the body's metabolism Testosterone Replacement Therapy (TRT) is a medical treatment for men who have low testosterone levels, a condition known as hypogonadism TRT aims to restore hormone levels to a normal range, improving symptoms associated with testosterone deficiency. Male hypogonadism is a clinical syndrome caused by androgen deficiency health (Figure 11) (Racaru-Honciuc *et al.*, 2014; Diamanti-Kandarakiset *et al.*, 2017; Handelsman, 2017; Moreau *et al.*, 2020; Rosenthal *et al.*, 2020; Matthew *et al.*, 2021; Wang *et al.*, 2021; Tramontano, 2023; Duet *al. al.*, 2024; Pontes Neto, 2024).

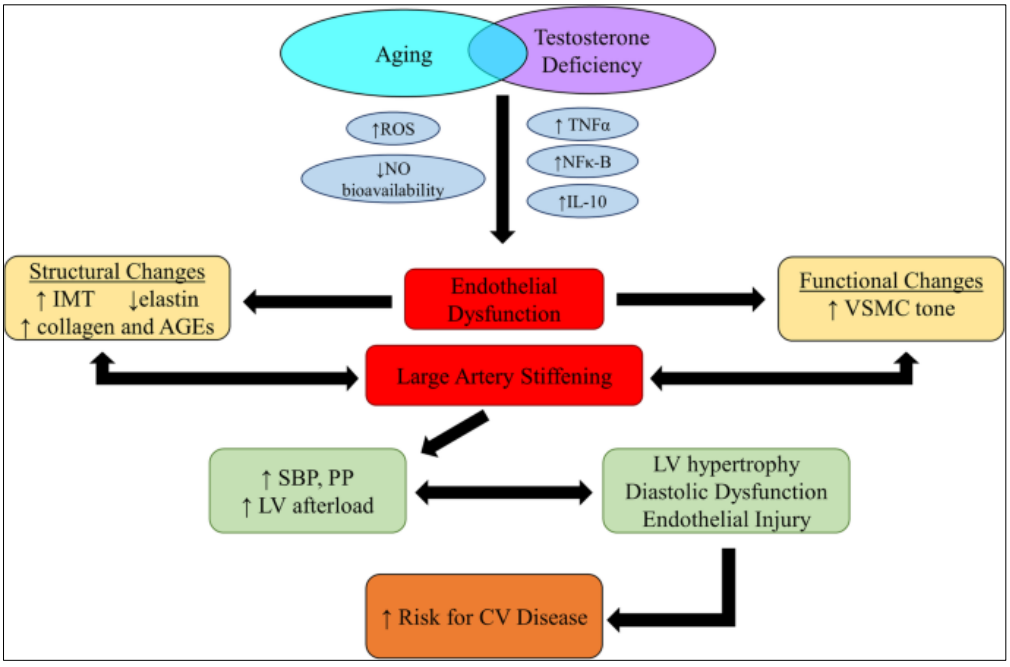

Figure 11: Mecanismos hipotéticos pelos quais a deficiência de testosterona pode contribuir para o envelhecimento vascular em mulheres e homens. AGEs, produtos finais de glicação avançada; CV, cardiovascular; IL-10, interleucina-10; IMT, espessura íntima-média; LV, ventrículo esquerdo; NFκ-B, fator nuclear κ-B; NO, óxido nítrico; PP, pressão de pulso; PAS, pressão arterial sistólica; ROS, espécies reativas de oxigênio; TNFα, fator de necrose tumoral-α, VSMC, célula muscular lisa vascular
Source: Doi: https://doi.org/10.1186/s13293-020-00294-8

Low levels of circulating androgens can cause disturbances in sexual development, resulting in congenital abnormalities of the reproductive tract. With advancing age, it can cause reduced fertility, sexual dysfunction, decline in muscle strength, decreased bone mineralization, lipid metabolism disturbance, and cognitive dysfunction. Androgen deficiency increases with age: an annual decline of 0.4-2.0% in circulating testosterone has been reported. In middle-aged men, the incidence is 6%. It is more prevalent in elderly, obese

men, and those with multiple comorbidities and poor health (Racaru-Honciuc *et al.,* 2014; Diamanti-Kandarakiset *et al.*, 2017; Handelsman, 2017; Rosenthal *et al.,* 2020; Matthew *et al.,* 2021; Wang *et al.,* 2021; Tramontano, 2023; Duet *al. al.,* 2024; Pontes Neto, 2024).

Testosterone Replacement Therapy (TRT) in women should only be performed when there is a well-established diagnosis of hypoactive sexual desire. This sexual dysfunction is defined based on clinical criteria, including changes in different elements of sexual function, such as arousal, desire, orgasm, and pain during sexual intercourse. Men with consistently low testosterone and who experience symptoms such as fatigue, loss of muscle mass, increased body fat, decreased libido, concentration problems, and depressed mood may be candidates for TRT (Figure 12) (Racaru-Honciuc *et al.,* 2014; Diamanti-Kandarakiset *et al.*, 2017; Handelsman, 2017).

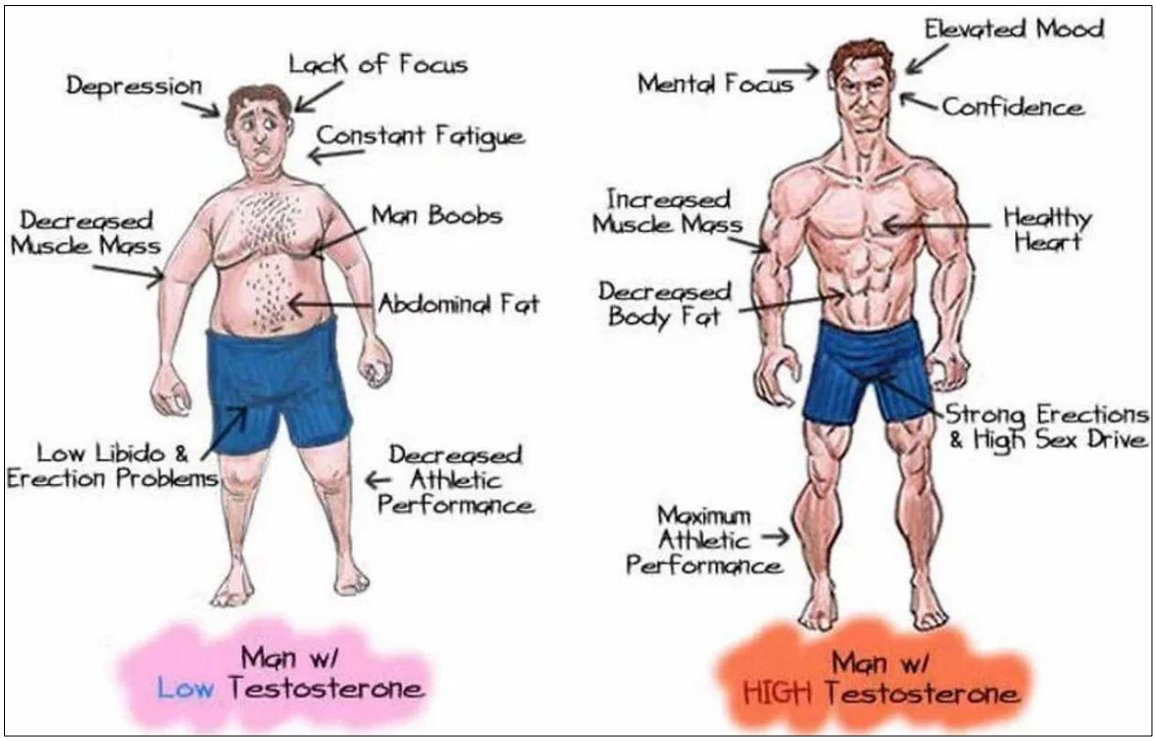

Figure 12: What is andropause? Just as females go through biological changes (menopause) as they grow older, men experience changes as well. As men age, levels of free testosterone decrease. This age-related decrease in testosterone production and levels is referred to as andropause. Unlike women, where a significant hormone change occurs within a short period, this hormone change in men can span over a long period. Andropause can start as early as mid-30s - early 40s

Source: https://mountainriverhealth.net/testosterone-replacement

A thorough medical evaluation is necessary to determine the appropriateness of treatment. TRT can be administered in a variety of ways, including intramuscular injections, transdermal gels or patches, subcutaneous implants, and buccal tablets. The choice of method depends on individual preferences, convenience, effectiveness, and potential side effects. When administered under medical supervision, TRT can be safe and effective. However, like any treatment, it can have side effects and risks, such as changes in cholesterol, increased risk of sleep apnea, and potential effects on the prostate. Detailed discussions with a healthcare professional are essential to understand the risks and benefits (Rosenthal *et al.,* 2020; Matthew *et al.,* 2021; Wang *et al.,* 2021; Tramontano, 2023; Duet *et al.*, 2024; Pontes Neto, 2024).

TRT can negatively affect fertility by suppressing sperm production. Men who wish to preserve their fertility should discuss treatment options and fertility preservation strategies with their doctor. The effects of TRT may begin to be noticed within 3 to 6 weeks, with improvements in energy, mood, and libido. However, changes in body composition, such as increased muscle mass and reduced fat, may take 3 to 6 months or longer. Depending on the underlying cause of testosterone deficiency, TRT may be necessary for a long time. Stopping treatment may result in the return of symptoms. A healthcare professional should regularly

assess the need to continue TRT. Monitoring includes regular symptom assessments, blood tests to check testosterone levels, and other laboratory tests to monitor for side effects. Dosage adjustments may be necessary based on the results (Figure 13) (Racaru-Honciuc *et al.*, 2014; Diamanti-Kandarakiset *et al*., 2017; Handelsman, 2017; Rosenthal *et al.*, 2020; Matthew *et al.*, 2021; Wang *et al.*, 2021; Tramontano, 2023; Duet *et al.*, 2024; Pontes Neto, 2024).

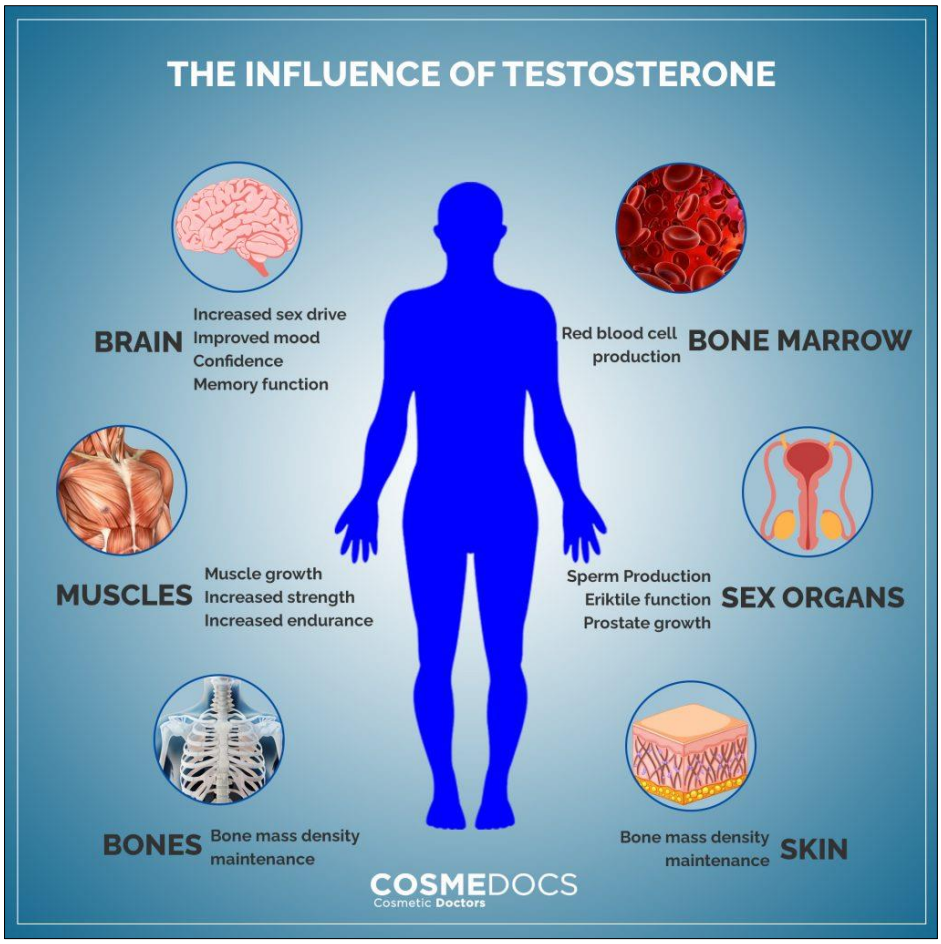

Figure 13: Testosterone Replacement Therapy England: TRT means testosterone replacement therapy; Androgen replacement therapy is another name for this treatment. However, as men get older, their testosterone levels decrease. This is known as andropause or male menopause, and the most frequent therapy is Testosterone Replacement Therapy or TRT. However, HRT implies female menopause, and this is the male version. Male menopause is less discussed and underestimated. Its most common purpose is to manage reduced testosterone levels, which may arise due to aging or medical issues
Source: https://www.cosmedocs.com/blog/trt-uk/

Hormone replacement therapy represents opportunities for more energy and health for many patients. When examining and performing hormonal balance in many of them, the prescription of bioidentical hormones may be indicated. One of these hormones is testosterone. For both men and women, the production of this hormone by the body tends to decrease as the years go by. In men, testosterone is one of the main natural anabolic steroids responsible for restoring numerous functions of the body. It is a great illusion to think that testosterone is a hormone only related to aspects of the sexual sphere (Rosenthal *et al.*, 2020; Matthew *et al.*, 2021; Wang *et al.*, 2021; Tramontano, 2023; Pontes Neto, 2024; Duet *et al.*, 2024).

3.5. Testosterone is key to Male longevity.

How to stay young and live longer longevity. Researchers look to genes, cells, hormones, eating patterns, and other factors for clues about what causes aging and how to prevent or slow it down. Research has identified three strategies that can help people live longer: Exercise. Follow certain types of diets. Eat fewer calories (BBC Brasil, 2007; Stefanacci, 2024c).

A study conducted by the University of California in the United States revealed that low testosterone levels can increase the chances of death among men over 50. The research, which analyzed 800 participants between the ages of 50 and 91, estimates that those with low doses of the male hormone are up to 33% more likely to die within 18 years than those with normal levels. The researchers said that 29% of those analyzed had low doses of testosterone, which is responsible for the development of male characteristics, including libido. The scholars explained that the amount of the hormone normally decreases with age, but that a healthy lifestyle can help maintain high testosterone levels and increase longevity (BBC Brasil.com., 2007; Matthew *et al.*, 2021; Wang *et al.*, 2021; Tramontano, 2023; Duet *al. al.*, 2024; Pontes Neto, 2024).

Emerging evidence suggests a crucial link between the Dietary Inflammation Index and various health outcomes, particularly concerning aging-related symptoms including mortality, cancer, cardiovascular diseases, musculoskeletal disorders, and mental well-being. The existing research strongly suggests that a low dietary inflammation Index, diet plays a significant role in delaying aging and reducing aging-related symptoms. Aging is a biological process of great complexity, the fundamental mechanisms of which are not yet clarified. It would therefore be too simplistic to reduce aging to simple hormonal deficiencies, which would be sufficient to compensate for to slow down, or even stop, the inexorable evolution, in an illusory search for an "eternal fountain of youth" (Figure 14) (Racaru-Honciuc *et al.*, 2014; Diamanti-Kandarakiset *et al*., 2017; Handelsman, 2017; Mohammadi-Shemirani *et al.*, 2020; Rosenthal *et al.*, 2020; Matthew *et al.*, 2021; Wang *et al.*, 2021; Tramontano, 2023; Pontes Neto, 2024).

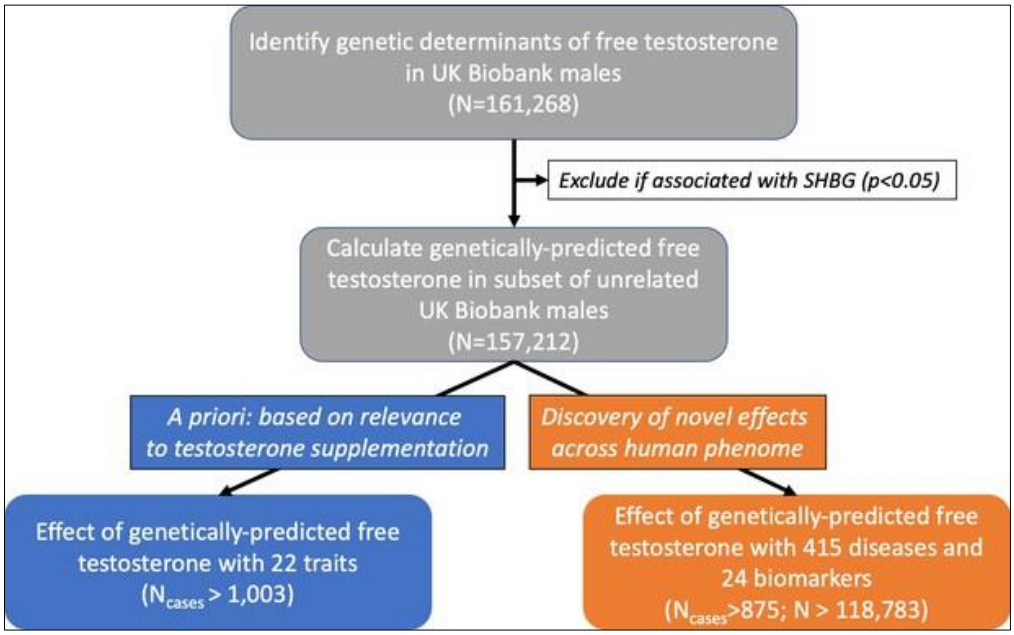

Figure 14: Free testosterone levels were calculated in males from the UK Biobank cohort. Then, genetic variants were tested for association with levels of CFT and carried forward if: genome-wide significant ($p<5\times10^{-8}$) and unassociated with SHBG ($p<0.05$). In the subset of unrelated males, these genetic variants were used to investigate the effect of genetically predicted CFT on (1) 22 a priori outcomes relevant to suspected effects of testosterone treatment using Mendelian randomization, and (2) 439 outcomes in a hypothesis-free approach using a weighted genetic risk score. CFT calculated free testosterone; MR, Mendelian randomization; SHBG, sex hormone-binding globulin

Source: Doi: https://doi.org/10.7554/eLife.58914

Considering the changes in the functionality of the endocrine system in the elderly, it is important to distinguish between the effect of physiological aging per se and that of age-related diseases in geriatric patients. The effects of a series of hormonal deficiencies likely to occur in the elderly are insufficient secretion of insulin, thyroid hormones, growth hormone, dehydroepiandrosterone, and testosterone. A loss of physiological function, a natural phenomenon that does not necessarily have repercussions on health and should not be compensated by the administration of hormones with the sole aim of restoring a level comparable to that measured in young subjects, and a pathological failure that merits supplementary treatment to correct the hormonal deficiency and improve the health of the elderly person (Racaru-Honciuc *et al.*, 2014; Diamanti-

Kandarakiset *et al*., 2017; Handelsman, 2017; Rosenthal *et al.,* 2020; Matthew *et al.,* 2021; Wang *et al.,* 2021; Tramontano, 2023; Duet *al. al.*, 2024).

4. DOES USING TESTOSTERONE HAVE A RISK RELATED TO PROSTATE CANCER?

Hormone replacement therapy (TRT) in cases of Androgen Deficiency in Male Aging (DAEM) affects prostate cancer. Studies have shown that hormone replacement therapy with testosterone does not pose a risk of developing prostate cancer in men who receive the hormone (Cunha *et al.,* 2024; Trovao, 2024).

4.1. Benefits of Testosterone Replacement Therapy (TRT)

4.1.1. Immune Strengthening

4.1.2. Prevention of Obesity

4.1.3. Ability of Exercise to Modulate Hormone Levels

4.1.4. Reduction of Stress

The most widely accepted theory today is that prostate cancer, once established, as androgen receptors mediate its behavior, may indeed worsen with androgen stimulation, but androgen stimulation will never be the promoter of receptor alteration, that is, TRT does not cause prostate cancer, but individuals with untreated prostate cancer could initially worsen with TRT. There is currently safety in performing TRT even in men who have been curatively treated for prostate cancer. The reduce study, a large study linking the effect of dutasteride in reducing prostate cancer in men, did not reveal any link between increased prostate cancer and circulating T or 5 alpha reductase levels (Isaacs and Isaacs, 2004; Andriole, 2009; Morgentaler and Traish, 2009; TJDFT, 2017; Traish, 2024).

For more than 60 years, medical specialties and Urology have always seen, as supposedly certain, the correlation between high testosterone levels and increased risk of prostate cancer. However, several studies around the world have been conducted and show data that are changing this paradigm, that is, demonstrating that there is no risk of developing prostate cancer in men who receive the hormone. “There is a complete lack of scientific data to support the idea that elevated testosterone is associated with an increased risk of prostate cancer. Specifically, no increase in prostate cancer has been noted when testosterone supplementation was given to patients who needed it” [Urologist Dr. Abraham Morgentaler of Harvard Medical School in Boston, USA] (Facio Jr, 2016).

"Our message aims to highlight the existence of safe and effective treatments on a subject that is still full of doubts and that interests the vast majority of men with low testosterone levels. Studies, such as those of Dr. Morgentaler, have emerged to break myths and prejudices regarding testosterone replacement therapy, which helps improve the quality of life of many men who previously suffered and experienced the great difficulties of prostate cancer treatment and are now survivors, and can take advantage of the opportunity to improve their sexual intimacy with their partner" (Facio Jr, 2016).

The American Urological Society says that doctors should inform patients about the lack of evidence linking testosterone therapy to the development of prostate cancer (Journal Estado de Minas, 2022).

4.2. Indications for testosterone replacement therapy:

4.2.1. Family History of Prostate Cancer

4.2.2. Locally Advanced Prostate Cancer

4.2.3. Breast Cancer in Men

4.2.4. Men Who Want to have Children

4.2.5. Hematocrit Greater than 54%

4.2.6. Severe Chronic Heart Disease

4.2.7. PSA Greater Than 4 Ng/Ml (Santella *Et Al.*, 2019; Fonseca, 2024)

The study conducted by Trovao (2024) shed light on the issue of the safety of TRT in the prostate, a common concern among physicians and patients. It also showed the safety of transdermal testosterone replacement, even among older men. Despite the classic contraindication to the use of testosterone replacement therapy (TRT) in men diagnosed with or suspected of having Prostate Carcinoma (PCa), there is no convincing evidence that normalizing serum testosterone levels in men with low levels is harmful (Rhoden and Averbeck, 2009).

5. CONCLUSION

Considering the changes in the functionality of the endocrine system in the elderly, it is important to distinguish between the effect of physiological aging per se and that of age-related diseases in geriatric patients. Testosterone replacement significantly increases the production of muscle tissue, causes a reduction in adipogenesis, reverses andropause symptoms, and increases longevity and psychological and emotional health. The administration of hormones to restore a level comparable to that measured in young individuals is a defect that deserves supplementary treatment to correct the hormonal deficiency and improve the health of the elderly.

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