The Multiple Health Benefits of Testosterone

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By

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FOREWORD

The male hormone testosterone affects men's lives in many ways. Not only does this hormone regulate our energy, passion, motivation, and libido, it also plays a crucial role in keeping our bodies healthy. When testosterone levels decrease in men as they age, several mechanisms regulating important body functions such as metabolic and cardiovascular functions are downregulated, facilitating the onset of metabolic and cardiovascular diseases. It seems like the number of people suffering from metabolic and cardiovascular diseases is increasing every year in our modern society, probably not solely due to age but also lifestyle adaptations such as sedentary work, processed food, and increased stress levels. All those factors can also affect testosterone levels. Physical activity, sun exposure, risk exposure, smoking, alcohol consumption, food, and many more factors can regulate our testosterone levels.

Some theories state that high levels of testosterone were given to men so they could hunt, protect and feed their families. Indeed, testosterone is associated with muscle mass and strength and also performance. As men aged, the role of conceiving and providing for the family was passed over to the younger generation and the body might have naturally adapted to this change from active to passive lifestyle by downregulating testosterone production. However, in addition to this natural age-related decrease in testosterone, as we observe a switch from a hunting, manual labor, and meat and natural food-based society to a computerized, sedentary, and processed food based society, men's organisms might have adapted to this new lifestyle in which hunter and survival instincts have become obsolete for the most part by downregulating testosterone levels, leading to a softer type of men with lower levels of testosterone.

Appearance and character traits seem to be strongly affected by the male hormone testosterone. Willingness to take risks, leadership and generosity are all traits of men with high levels of testosterone. Concerning appearance, men with high levels of testosterone tend to have a muscular body, strong jawlines, and thick body hair. Testosterone does not only change through environmental adaptations but also decreases as men age. Interestingly, energy levels, muscle mass/strength, libido, and mobility decrease in

parallel with testosterone levels in men. Testosterone appears to be the energy source in men which slowly declines with aging. As we age, our body seems to be programmed to decrease the production of testosterone and pull the breaks to an active lifestyle. It seems like our body is trying to tell us to slow down and get ready for retirement. As testosterone takes a deep dive around the age of 60, men seem to get banned from work, physical and sexual activities, doomed to lead a boring, frail life. The common consensus seems to be that elderly men are supposed to stay home, be calm and frail. And on top of that, getting chronic diseases like metabolic syndrome, type 2 diabetes, cardiovascular diseases, erectile dysfunction, osteoporosis, and arthritis seems to have become an acceptable outcome for elderly men. Even though it seems clear that decreases in testosterone levels are associated with not only the decline in energy and quality in life but also the increase in chronic diseases in elderly men, many pharmaceutical companies, physicians, and regulatory bodies seem to stick to conservative rules protecting the established treatments for each chronic disease with expensive treatments instead of liberalizing the use of testosterone replacement therapy and prevent those chronic diseases. Conservative legislation in many countries still prevents access to testosterone treatment to many people suffering from hypogonadism, leaving those patients untreated and prone to several chronic diseases associated with low testosterone levels. In many countries, the governmental bodies in charge of health care regulations and health professionals might need to update their knowledge on testosterone and understand the importance of this hormone in maintaining the male body healthy during the aging process.

Several attempts to demonize testosterone replacement therapy have been made displaying results associating testosterone with prostate cancer or cardiovascular diseases. However, these data have not only been proven wrong but it has been shown by recent research that low testosterone negatively affects these conditions. Replacing lacking things seems natural, especially when it comes to our health. The shelves of pharmacies and supermarkets are filled with supplements of all kinds. However, when it comes to testosterone, just because testosterone is associated with increased energy and libido seems to be taboo in our society. Do elderly men not have the right to replace their lacking testosterone to improve their quality of life? To prevent the onset of chronic diseases? Are aging men doomed to lead a boring, diseased life? Why does society not let men improve their quality of life? For pharmaceutical companies and health care providers, it is much more lucrative to treat people suffering from diabetes, osteoporosis, and cardiovascular diseases with several expensive drugs for the rest of their life rather than prescribing affordable testosterone to prevent the onset of these

diseases. Testosterone is a naturally occurring hormone released inside our body, replacing a lack of this hormone to restore healthy levels and optimize metabolic and cardiovascular functions seems obvious, however current practice seems to prefer practicing polypharmacy and administer several chemicals unknown to the human body in order to sustain an impaired system instead of curing the cause.

Regulations with regard to testosterone prescription differ quite a bit depending on the country. Some countries still treat testosterone like a dangerous drug and prescription is very cumbersome and therefore testosterone therapy often does not reach the patients who could benefit from it. Even though testosterone is a major regulator of several pathways in the male body, most health checkups, and insurance coverage do not include tests for serum testosterone. Many general practitioners are not aware of the important role testosterone has in the male body and that decreases of this hormone could be causes for impairments in metabolic, cardiovascular, or neurological functions. Research on the benefits of testosterone in elderly men has dramatically advanced within the last decade and there is a need to instruct general practitioners and physicians specializing in chronic diseases affected by testosterone levels about the new insights we have on the effects of testosterone. Regulatory bodies and insurance policies should also update their regulations so that patients needing testosterone can get diagnosed and get access to testosterone treatment before the onset of potential chronic diseases. The author of this book strived to summarize the newest research on testosterone replacement therapy with regard to several diseases in men in order to provide one complete reference book on testosterone replacement therapy. The authors would also like to express their gratitude to all the researchers who are cited in this book for all their amazing work contributing to the improvement of men's health.

INTRODUCTION

No other drug has been as controversial as testosterone. Since its discovery in the 1930s, this drug changed its image several times from a novel drug curing hypogonadism to a doping agent used by athletes and bodybuilders to increase muscle mass to a “sex drug” used by senior males to enhance their sex drive and performance to a very dangerous drug with multiple side effects leading to prostate cancer to finally become a “miracle medication” with the potential to treat several severe diseases with minimal side effects.

Nowadays, testosterone's health benefits are widely acknowledged and major improvements in the quality of life involving physiological, psychological, and sexual aspects have been attributed to testosterone replacement therapy in low testosterone patients (Rosen et al. 2017). Besides general improvements in the quality of life, we see more and more studies investigating the effects of testosterone on several conditions such as obesity, diabetes, osteoporosis, arthritis, and depression. Testosterone has been demonized as a dangerous drug leading to prostate cancer and cardiovascular diseases for decades, however recent research demonstrated that it is quite the opposite. Testosterone replacement therapy has been shown to improve prostate and cardiovascular health in hypogonadal males, rejecting the theories of severe side effects of testosterone replacement therapy believed in the past.

In the last decade, testosterone has been shown to improve conditions related to obesity and diabetes (lean body mass increase, Hb1Ac decrease, triglyceride decrease), osteoporosis (increase in bone mineral density), arthritis (decreased inflammation), sarcopenia (muscle mass increase) and cognitive impairments (increased neuroprotective functions) without major side effects. A recent study even showed that testosterone improves proliferation and preserves stemness of human adult mesenchymal stem cells and endothelial progenitor cells, suggesting novel potential therapeutic fields of testosterone (Corotchi et al. 2016). Furthermore low levels of testosterone seem to be correlated with liver disease and low levels of testosterone might worsen cirrhosis in male patients (Sinclair et al. 2015).

Unlike other medications used to treat the conditions mentioned above, testosterone is a naturally occurring hormone endogenously produced mainly in the testicles in males. Testosterone has a very complex mechanism of action; it has genomic mechanisms, non-genomic mechanisms, and indirect effects via aromatase converting testosterone into estradiol or 5αreductase converting testosterone into DHT. Low testosterone levels might lead to impaired body functions, therefore replacement of this hormone to natural levels is critical in order to maintain healthy body functions in aging males. However, to this day, the general population still often considers testosterone as an androgenic anabolic steroid associated with several side effects such as prostate enlargement/ cancer, cardiovascular diseases, acne, infertility, and gynecomastia. This image is probably due to athletes abusing this hormone and taking it in enormous supraphysiological doses. Like with every other hormone in the body, overdosage way beyond physiological levels will probably lead to side effects. Therefore it is important to differentiate between replacement doses and supraphysiological doses. Even though the association of testosterone with obesity and type 2 diabetes is well known, still many physicians neglect testosterone levels in the assessment of patients' health conditions. Indeed, in a general blood test total testosterone or free testosterone levels are often omitted. However, it might be the case that a condition due to low testosterone is treated with different drugs because the patient was not tested for testosterone levels. In this case, testosterone treatment could be much more natural and efficient. Furthermore, the general knowledge about the benefits and risks of testosterone replacement therapy is still low within the general population (Gilbert et al. 2017). Currently, testosterone tests are often not covered by insurance in many countries except for urology-related treatments such as hypogonadism, prostate cancer, or other related conditions. On the other hand, patients seeking advice for metabolic, cardiovascular, bone, depression, anxiety, or joint-related conditions do often not get assessed for testosterone levels. The main goal of this book is to increase the awareness of a broad range of health professionals with regard to the importance of testosterone in the regulation of several diseases. With an increasing number of health professionals understanding the implications of low testosterone levels, many arising conditions might get detected at an early stage and potentially prevented or treated with testosterone replacement therapy.

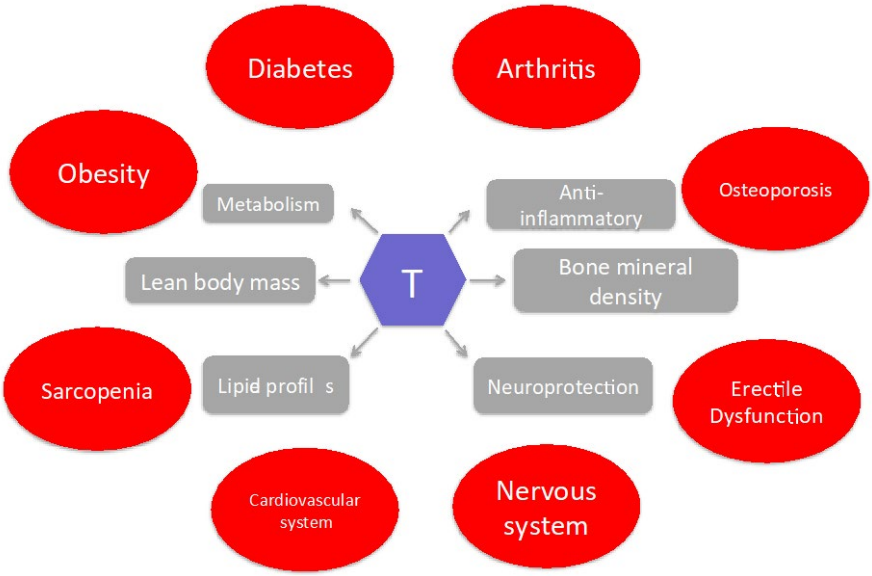


Figure 1. Representation of the numerous positive effects of testosterone on several diseases

1

HISTORY OF TESTOSTERONE

Loss of virility and fertility via loss of the testes or testicular functions is obvious and the consequences were known since antiquity even before the discovery of sperm and their function in the 17th and 18th centuries and the isolation and synthetic production of testosterone in the 20th century (Nieschlag et al., 2019).

Aristotle already described the generation of visible organs in fertilized chicken eggs *in The Generation of Animals* and depicted the effects of castration in men.

But in reality, castration was used to create obedient slaves a long time before that Ming dynasty (1368–1644). In Islamic societies, castrated slaves were used in elite troops to fight wars of conquest.

In Scandinavia, treaters were castrated and blinded, a method also adopted by the Normans and William the Conqueror who replaced the Anglo-Saxon death penalty by castration and blinding.

Castration also was used to maintain the voice of boys high in order to produce soprano and alto voices with the acoustic volume of an adult male for operas in the 17th and 18th centuries. Interestingly, castration was also used for the treatment of leprosy, epilepsy, gout, priapism, excessive masturbation, and insanity during Greek-Roman times and the Middle Ages, showing a lack of knowledge with regard to the effects of castration during this period.

The first physician who discovered the functions of testes was Arnold Adolph Berthold (1803–1861) from the University of Göttingen, Germany, who witnessed the restoration of androgenic functions via transplantation of testes from roosters to capons. He hypothesized that the testes affect the blood and the organism as a whole, making him the first to propose systemic effects of the testes on several different distant organs, which led to his name as 'Father of Endocrinology'. During the same period, the anatomist Franz

Leydig (1821–1908) from the University of Würzburg depicted the interstitial Leydig cells in the testes. However, he did not fully comprehend their function at this time.

In 1909, Moritz Nussbaum, followed by Eugen Steinach in Vienna in 1910 and A. Pézard in Paris in 1911 reproduced Berthold's experiments on several animals and confirmed his findings.

During the same period, Ancel and Bouin proposed an endocrine function for the Leydig cells as follows: 'In numerous previous studies, we have assembled a group of morphological, physiological and chemical facts that, taken together, allow us to formulate the following hypothesis: that the general action of the testes on the organism, ascribed in the past to the testes as a whole, is actually due to the interstitial gland.

Shortly later, physicians tried to treat hypogonadism, anti-aging, and several other conditions via testes transplantation. In 1913, Victor D. Lespinase revealed his trials involving the transplantation of human testes from donors to patients for rejuvenation purposes. In 1915, George Frank Lydston from Chicago 1915 started to transplant testes from accident victims to patients. Also in Chicago, Leo Stanley from the California State Prison San Quentin revealed 20 cases of transplantation of testes from executed prisoners to other inmates experiencing signs of revitalization in 1923.

John Romulus Brinkly started a business involving goat testis transplantation in Milford, Kansas between 1918 and 1930 until a Texan judge declared him guilty of charlatanism in 1939. In the meantime, in In Vienna, Eugen Steinach recommended physicians perform unilateral vasoligation for rejuvenation goals. Serge Voronoff started xenotransplantation with monkey testes for rejuvenation. After being active in Paris for a while, several scandals led him to pursue his operations in Algiers, where patients from all over the world came to seek his treatment. In 1927 the Royal Society of Medicine (London) declared Voronoff's claims as false.

However, all these scandals and the advance in steroid biochemistry finally led to the discovery and synthesis of the male sex hormone.

Nevertheless, before the discovery of synthetic testosterone, the powerful function of the testes in men led patients to ingest these organs in many different ways. In Rome, Gaius Plinius Secundus (23–79) recommended the consumption of animal testes in order to cure hypogonadism and impotence

while the Arabic physician Mesue the Elder (777–837) in Baghdad prescribed testis extracts. In Chinese medicine, Hsue Shu-Wei recommended raw and desiccated animal testes whereas the 'Universal Doctor' and founder of the University of Cologne, Albertus Magnus (1192–1280), prescribed powdered hog testes dissolved in wine.

Until recently, tablets containing similar ingredients continued to be on the market. Ingredients such as testis extracts, yohimbine, and *testis sicca*. However, in contrast to other endocrine glands such as the thyroid or pancreas, the testes do not store testosterone. An adult man would have to eat about 1 kg of (bull) testes to reach the average endogenous production of 6–8 mg/day of testosterone. Furthermore, even if this amount of testosterone in form of bull testes would be ingested, the testosterone taken orally would be broken down during the first-pass effect in the liver. However, this type of testicular organ therapy administered orally could have placebo effects.

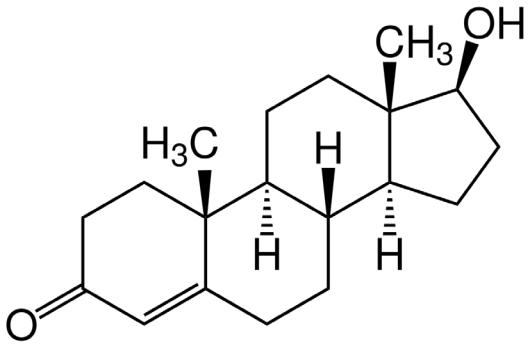
Even though synthetic testosterone was already available, several companies worldwide such as Ciba (Switzerland) continued producing Androstin® ('biologically titrated full extract from male gonads' for oral and parenteral use) until 1961.

Organotherapy became very popular at the end of the late 19th and early 20th centuries. During this time, Charles E Brown-Séquard (1847–1894), revealed the results of his self-experimentation in the *Lancet* 1889. He self-administered 1-mL injections of a mixture of one part testicular vein blood, one part semen, and one part juice extracted from a dog or guinea-pig testes daily. After 20 days, he observed the following: 'A radical change took place in me … I had regained at least all the strength I possessed a good many years ago. I was able to make experiments for several hours. After dinner, I was able to write a paper on a difficult subject. My limbs, tested with a dynamometer, gained 6 to 7 kg in strength. The jet of urine and the power of defecation became stronger'. Leading to exploding sales of extracts of animal organs by the Brown-Séquard method.

With the advance in steroid biochemistry, researchers discovered the ring structure of steroids and bile acids at the National Institute of Medical Research in London in 1932 and at the Bavarian Academy of Sciences in Munich also in 1932. Under the sponsorship of the Health Organisation of the League of Nations (the predecessor of WHO), a team of chemists including Edmund A Doisy, Adolf Butenandt, and Guy Marrian gathered at the University College London and came to the consensus that steroids had

four rings and the fourth ring had five C-atoms. The same team of researchers, including Ernest Laqueur, also had isolated pregnanediol and estrone from pregnant mare urine. In 1934 Butenandt and his colleagues added progesterone to the list of sex steroids, aiming to replace organotherapy and to create steroid substitution to treat patients.

In 1931, Adolf Butenandt, then at the University of Göttingen, extracted 15mg of the androgenic steroid androsterone (androstan-3α-ol-17-one) from 15,000 L of urine. In 1935 in the Netherlands, Ernst Laqueur (1866–1947) and his group at the University of Amsterdam and Organon isolated 10 mg of a different androgen (17β-hydroxy-4-androstene-3one) from 100 kg of bull testes, a compound of the composition $C_{19}H_{28}O_2$ which they named "testosterone". During the same time, Butenandt (Göttingen) and Hanisch (Gdansk) as well as Ruzicka (Zürich) and Wettstein (Basel) succeeded in synthesizing testosterone; on this basis Butenandt suggested the correct structural formula of testosterone.



In 1935, several pharmaceutical companies such as Ciba (Switzerland), Schering-Kahlbaum (Germany), Boehringer (Germany), Chimio Roussel (France), and Organon (The Netherlands) started to share their knowledge forming a market-leading syndicate.

Due to its liposoluble chemical composition, testosterone was first developed as subcutaneous pellets or with an added 17α-methyl group to make it orally active. However, due to its liver toxicity, the injectable form of esterified testosterone enanthate or cypionate replaced the oral methylated version in the 1950s and allowed patients infrequent injections every 2-3 weeks. The enanthate and cypionate esters with a half-life of approximately 4.5/5 days respectively, allow injections every 2-3 weeks due to their long ester, slowly releasing testosterone into the bloodstream.

Several different esters have been developed since, allowing more or less frequent injections. For instance, the propionate is the fastest one with a half-life of 0.8 days and demands daily or every other day injections in order to keep stable serum values. The phenylpropionate ester has a half-life of 1.5 days, the isocaproate ester 4 days, and the decanoate ester half-life is 7.5 days). Mixtures of different esters have been developed to keep stable testosterone levels with minimal injections due to the long esters and to "kick-start" its action with the short esters. Recently transdermal gel has also been developed to accommodate patients reluctant to injections. However, this method of application requires daily use and the risk of transfer to other people via skin contact. Another new form of administration is the nasal form, allowing easy and quick application and without the risk of transfer to other people or the pain from injections. One study comparing the effects of the hormone depending on its form of administration has shown that daily transdermal patches (2.5mg) led to more stable testosterone, estradiol, and dihydrotestosterone levels as compared to 200mg of intramuscular injections of testosterone enanthate every two weeks (Dobs et al. 1999). A recent study showed promising results for the nasal administration form (Rogol et al. 2016):

1) Low doses due to the high absorption rate (no first-pass metabolism)
2) Rapid
3) Non-invasive
4) Convenient
5) No secondary transference

Recently, a new type of oral testosterone undecanoate has been developed. This oral testosterone preparation is lymphatically delivered and showed promising results in test phases without the side effects on liver values commonly observed in oral testosterone administration (Patel et al. 2020). One preparation is already sold under the brand name Jatenzo®.

Also new to the market, a sub-cutaneous self-injection pen sold under the brand name Xyosted®, allows weekly or even more frequent injections at home, leading to less fluctuations in serum testosterone levels as compared with intramuscular injections administered at health care facilities every 2-4 weeks.

However, those new types of testosterone preparations tend to be expensive and often not covered by health insurance.

An average between 2.1 and 11.0 mg of endogenous testosterone is produced in healthy male adults (de Souza and Hallak 2011). Testosterone replacement therapy typically administers 75-100 mg per week or 150-200 mg every two weeks of testosterone (Bhasin et al. 2010) cypionate or enanthate which should lead to levels within the average mid-normal physiological range (400 to 700 ng/dL) (Shoskes et al. 2016).

The use of testosterone in the male population over 30 years in the United States steadily increased from 2002 to 2013 where it reached a peak of 3% of this population after which it started to decrease (Baillargeon et al. 2018). The reason for this decline might be due to the release of 2 publications reporting adverse effects on cardiovascular health-related to testosterone (Finkle et al. 2014; Vigen et al. 2013). However, especially one of those publications got criticized with regard to a lack of quality and accuracy of the study (Bauchner and Vigen 2013; Vigen et al. 2013). Indeed this study has been shown to include major errors in reported values, namely the improper exclusion of 1132 men with prior MI or stroke history of myocardial infarction or stroke, which got corrected to 128 (Morgentaler et al. 2013). Furthermore, the number of men excluded for missing coronary anatomy was revised from 397 to 1301 (Morgentaler et al. 2013). Besides, it turned out that 100 women were included in the initial group of 1132 individuals (Morgentaler et al. 2013). The trend of the research is rather supporting the health benefits of testosterone with regard to several parameters including cardiovascular health (Traish et al. 2017a).

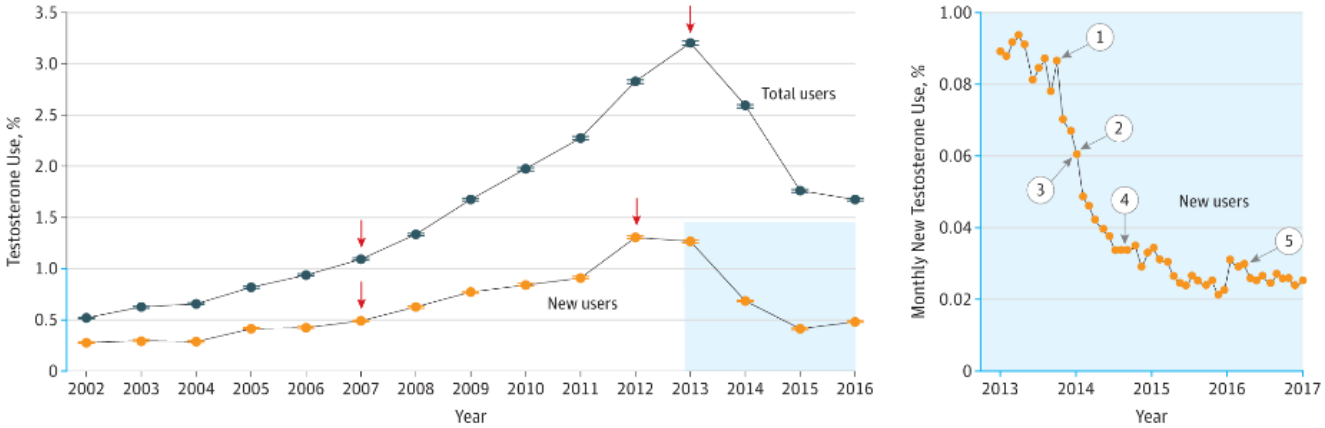


Figure 2. Total and New Testosterone Use Among Men 30 Years or Older in the United States, 2002-2016. Denominators were calculated for each calendar year. Each denominator included all men who were ≥30 years at the start of the calendar year with continuous benefits for the entire study year and prior year. The denominators range from 1 823 677 in 2002 to 2 856 954 in 2016. Error bars represent 95% CIs. Interrupted time series analysis with joinpoint regression was used to assess time-related trends in testosterone use. The analysis allowed for a maximum of 5 joinpoints (indicated by red arrows). For total testosterone users, joinpoints were located in 2007 (95% CI, 2005-2010) and 2013 (95% CI, 2012-2014). For new testosterone users, joinpoints were located in 2007 (95% CI, 2004-2012) and 2012 (95% CI, 2010-2014). The inset presents new testosterone prescription rates by month, from January 2013 through December 2016. Denominators for monthly rates included all men ≥ 30 years at the start of the month with continuous benefits for the entire month and the 12 previous months.

The listed numbers indicate the following specific dates: (1) article by Vigen et al released online November 6, 2013; (2) article by Finkle et al released online January 29, 2014; (3) US Food and Drug Administration (FDA) safety communication on testosterone therapy, January 31, 2014; (4) FDA advisory committee meeting on possible cardiovascular risks associated with testosterone therapy, September 17, 2014; (5) FDA requires testosterone label change indicating a possible increased risk of myocardial infarction and stroke, March 3, 2015.

From: Testosterone Prescribing in the United States, 2002-2016
JAMA. 2018;320(2):200-202. doi:10.1001/jama.2018.7999

The question arises if our modern society is facing decreases in male testosterone levels due to increasing obesity. Indeed, the expression of aromatase is higher in adipose tissue leading to increased conversion rates of testosterone to estradiol, signaling to the pituitary gland to reduce gonadotropin secretion and therefore reducing testosterone (Fink et al. 2018).

Due to the increasing number of convenient testosterone administration methods, the decrease of testosterone levels in males in our modern society, the increasing number of studies supporting the benefits of testosterone replacement therapy in a wide range of health conditions, application fields for testosterone, and its demand will probably be going to increase in the future.

2

CLINICAL APPLICATIONS OF TESTOSTERONE

In 2013, about 2.3 million American males were on testosterone replacement therapy. More than half of these testosterone prescriptions were made by primary care physicians. In the U.S., the percentage of men using TRT increased from 0.52% in 2002 to 1.67% in 2016, with a peak in use in 2013 (3.20%) (Baillargeon et al. 2018). The reason for the decrease since 2013 seems to be the publication of 2 studies in 2013 (Vigen et al. 2013) and 2014 (Finkle et al. 2014) reporting increased myocardial infarction and stroke associated with testosterone use and a safety bulletin issued by the Food and Drug Administration in 2014. However, recent research is not in line with these results and tends to show beneficial effects of TRT on cardiovascular health (Haider et al. 2016).

The main indication for testosterone replacement therapy is hypogonadism, a condition which can be categorized into either primary (Testes do not produce enough testosterone) or secondary (impaired hypothalamic-pituitary-gonadal axis (HPGA)) hypogonadism. Testosterone is synthesized in the Leydig cells in the testes via luteinizing hormone (LH) stimulation. Bound to its receptors in the Leydig cells, steroid activating receptor is activated and cholesterol to pregnenolone conversion starts via cholesterol transfer through the mitochondrial membrane. Testosterone is then synthesized in the endoplasmic reticulum. However, in aging males, LH action is impaired in the Leydig cells, leading to primary hypogonadism. On the other hand, aging-related decreased release of gonadotropin-releasing hormones (GnRH) which stimulate LH and follicle-stimulating hormone (Rosenstock et al.) can lead to impairments of the HPGA, known as secondary hypogonadism. Besides aging, the medical conditions below have been shown to induce low testosterone levels in males:

1) Obesity: Gonadotropin release is impaired in the pituitary via increased levels of estrogen triggered by elevated aromatase due to excess adipose tissue, leading to decreased testosterone secretion (Du Plessis et al. 2010).

2) Type 2 diabetes: Impaired glucose metabolism leads to fat accumulation triggering increased aromatase activity and negative feedback to the pituitary resulting in low testosterone production (Muraleedharan and Jones 2010).
3) Chronic obstructive pulmonary disease (COPD): Elevated prolactin levels in COPD patients might lead to impaired LH secretion (Mousavi et al. 2012).
4) Chronic kidney disease (CKD): Chronic inflamed state elevates inflammatory biomarkers which can trigger alterations in the HPGA (Carrero et al. 2009).
5) HIV: lymphoma or syphilis of the pituitary might lead to or mimic apoplexy, meningeal or pituitary infection inducing fibrosis and ultimately dysfunction (Wong et al. 2017).

In 2015, The U.S. Food and Drug Administration declared aging-related low testosterone treatment with testosterone replacement therapy as off-label use (Metzger and Burnett 2016; Petering and Brooks 2017). Therefore testosterone replacement therapy should only be prescribed in case of the presence of signs or symptoms of hypogonadism such as anemia, gynecomastia, depression, diminished bone density, decreased energy and or muscle mass, hot flashes, sweats, impaired cognition, incomplete or delayed sexual development, increased body fat, increased fatigue, infertility, loss of body hair, decreased libido and small testes (Petering and Brooks 2017). Diagnosis of male hypogonadism is usually made in several steps, simplified in the figure below (Figure 3). Depending on the physician or country, different parameters may be used.

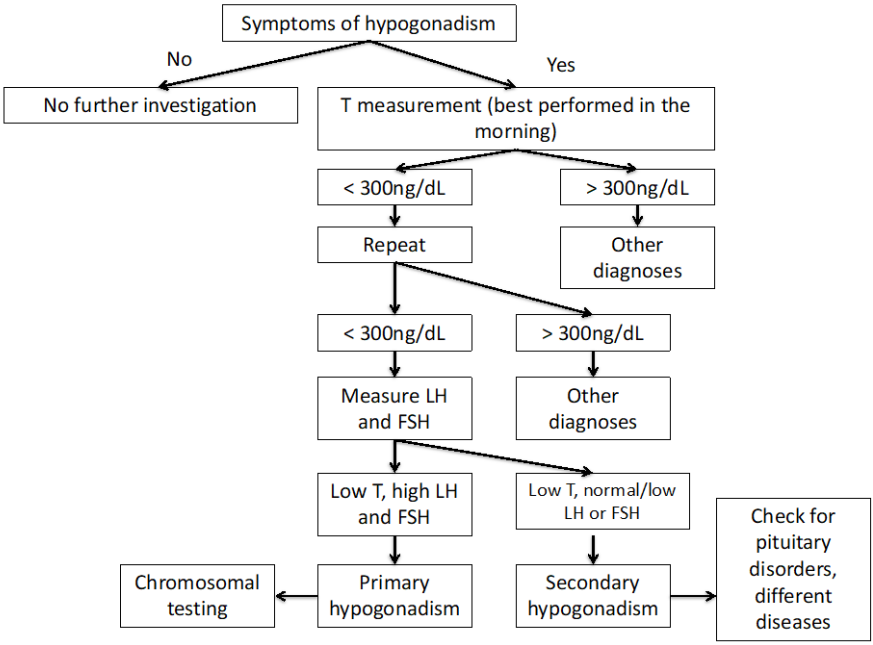


Figure 3. Simplified Diagnosis chart of male hypogonadism. T: testosterone, LH: luteinizing hormone, FSH: follicle-stimulating hormone.

As we can see from the above, testosterone replacement therapy is mainly used to treat primary and secondary hypogonadism. However, pituitary disorders may arise from a wide variety of other conditions such as diabetes, obesity, CKD, COPD, HIV, or post-operation pituitary tumors. Therefore, a broad screening of the patient's health condition is necessary to assess the necessity of testosterone replacement therapy. In some cases, testosterone deficits and the onset of other conditions can occur within a vicious circle. For instance, testosterone replacement therapy might benefit individuals prone to obesity, type 2 diabetes, osteoporosis, arthritis, and cognitive impairments. Including testosterone in a general health check might be useful to prevent and assess several diseases.

3

TESTOSTERONE AND OBESITY

Very often obesity goes hand in hand with hypogonadism. Due to increased adipose tissue, aromatase that converts testosterone into estradiol increases, inducing negative feedback to the pituitary gonadotropin secretion leading to a decrease in testosterone levels (Fui et al. 2014) (Figure 4).

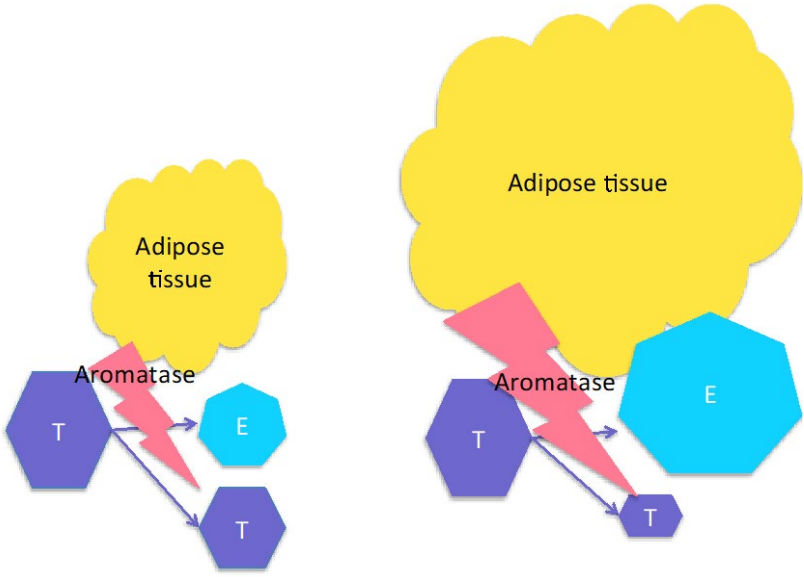


Figure 4. Increased estradiol (E) and decreased testosterone levels in excess adipose tissue leading to elevated aromatase activity.

Besides, a recent study demonstrated that suppression of the testicular leptin and JAK-STAT pathway, a decrease in serum testosterone to estradiol ratio, and sperm quality parameters occur in response to a high-fat diet (Yi et al. 2017) (Figure 5). Indeed excess adipose tissue can trigger pathological

impairments of the Leydig cells, oxidative stress in the testes, and elevated leptin levels leading to secondary hypogonadism (Zhao et al. 2014). Increased inflammation via the interleukin-1-receptor pathway might also induce obesity-related hypogonadism (Ebrahimi et al. 2017). We can extrapolate from the information above that testosterone production can be impaired via numerous different pathways triggered by excess adipose tissue.

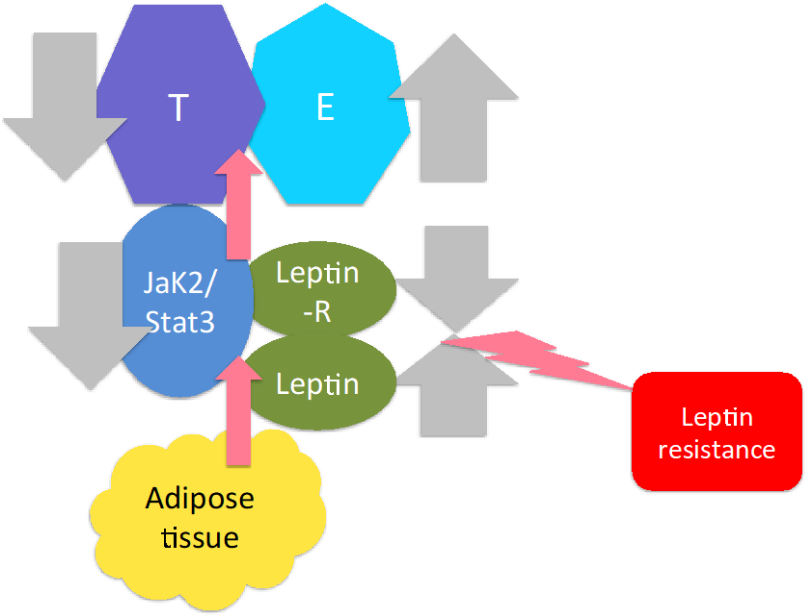


Figure 5. Adipose tissue-induced testosterone decrease/estradiol increase via JaK2/Stat3 increase and leptin increase coupled with a leptin receptor (Leptin-R) decrease.

Obesity is often linked to chronic low-grade inflammation. Interleukin-1 is a cytokine playing a key role in regulating the innate immune system. It has been demonstrated that inhibition of IL-1 improves glycemia, β-cell secretory function, and systemic inflammation markers (IL-6 and C-reactive protein (CRP)) in diabetic men (Larsen et al. 2007). A recent study showed that 4 weeks of treatment of obese hypogonadal males with an interleukin-1 (IL-1) antagonist (anakinra) leads to an increase in testosterone levels (Ebrahimi et al. 2018). On the other hand, treatment with testosterone for 30 weeks led to significant decreases in body weight, body mass index