REVIEW PAPER

JMS Journal of Medical Science

Impact of testosterone levels and testosterone replacement therapy on men's health

Zuzanna Karbowska*
Faculty of Medicine, Poznan University od Medical Sciences, Poland
Corresponding author: zuzanna.karbowska99@gmail.com

Katarzyna Cierpiszewska*
Faculty of Medicine, Poznan University of Medical Sciences, Poland

Klara Maruszczak*
Faculty of Medicine, Poznan University of Medical Sciences, Poland

Ivanna Sukhachova*
Faculty of Medicine, Poznan University of Medical Sciences, Poland

Dominika Szwankowska*
Faculty of Medicine, Poznan University of Medical Sciences, Poland

Igor Piotrowski
Department of Electroradiology, Poznan University of Medical Sciences, Poland; Radiobiology Laboratory, Department of Medical Physics, Greater Poland Cancer Centre, Poland
https://orcid.org/0000-0002-4985-9321

* Authors equally contributed to the study

doi: https://doi.org/10.20883/medical.e856

Keywords: testosterone, testosterone deficiency, functional hypogonadism, late-onset hypogonadism (LOH), testosterone replacement therapy (TRT)

Received 2023-05-17
Accepted 2023-09-22
Published 2023-12-07

How to Cite: Karbowska Z, Cierpiszewska K, Maruszczak K, Sukhachova I, Szwankowska D, Piotrowski I. Impact of testosterone levels and testosterone replacement therapy on men's health. Journal of Medical Science. 2024 March;93(1):e856. doi:10.20883/medical.e856

ABSTRACT

Various studies have shown that testosterone levels have a heavy impact on areas of a man's health. Low serum testosterone (and, by analogy, late-onset hypogonadism) may be responsible for such conditions as type 2 diabetes, obesity in the abdominal area, and, most of all, heightened cardiovascular risk (CV). Among other outcomes, researchers have pointed out metabolic syndrome and dyslipidemia, as well as an increased risk of anxiety disorders and major depressive disorders. There have also been reports of testosterone's influence on fertility, bone mineral density, and the development of polycythemia. Low testosterone can have a variety of effects, all of which increase the risk of premature death by raising inflammatory marker levels.
Overly high testosterone, however, has been proven to have a notable influence on men's personalities, as well as other psychological and social traits, both in endogenously elevated testosterone levels and in patients with a history of anabolic-androgenic steroid use.
The last decade's research on testosterone's impact on the organism has yielded contradictory results. Therefore, examination and understanding of the influence of its abnormal levels prove essential to not only guarantee the best quality of hypogonadism treatment but also to efficiently prevent any side effects or complications associated with testosterone use.

Introduction

Testosterone (T) is a steroid hormone influencing men's physiology. It is responsible for developing male sexual characteristics and maintaining them later in life. With age, however, levels of testosterone decline [1], which in approximately

5% of cases might lead to the development of late-onset hypogonadism (LOH) [2,19].

The definition of testosterone deficiency varies among researchers, who may need help forming consistent diagnoses for men affected by it. Therefore, it is essential to understand and clearly define the issue. A recent study by Salter et al. compared multiple guidelines for testosterone therapy produced by some of the major medical societies specializing in urology, endocrinology and sexual medicine and presented a consensus that testosterone deficiency is defined by abnormal laboratory results as well as clinical manifestations. Laboratory thresholds vary from as low as <10.4 nmol/L (American Urological Association) to <12.1 nmol/L (European Association of Urology, International Society for Sexual Medicine, International Society for the Study of the Aging Male). Some societies do not propose detailed levels, either not including them in the recommendations (American Association of Clinical Endocrinologists) or describing the measurements as 'consistently low' (Endocrine Society). British Society of Sexual Medicine and the European Association of Urology emphasise the importance of measuring total and free testosterone levels. Clinical signs mentioned by Salter et al. include anaemia, osteoporosis, infertility and erectile dysfunction, psychological symptoms, diabetes mellitus and muscle mass loss, all of which we will describe later in our review. Patients presenting such symptoms should undergo further examination [3]. European Academy of Andrology (EAA) highlights the importance of considering LOH a functional instead of an organic form of hypogonadism (caused by obesity and medication). It, therefore, suggests excluding organic causes of hypogonadism before diagnosing the patient [4].

Various studies have shown that LOH heavily impacts many areas of a man's health [5–10]. It is important to remember that as a functional disease, hypogonadism should be initially treated with lifestyle changes such as weight loss or withdrawal of drugs impairing the production of testosterone, if possible. EAA suggests testosterone replacement therapy's (TRT) positive influence on sexual function in hypogonadal men, but there is insufficient evidence regarding its positive impact on other outcomes [4].

In the face of the last decade's contradictory results of testosterone research [11], this review aims to analyse the most recent studies regarding testosterone level impact on male cardiovascular (CV), metabolic and psychological health. Moreover, we tried to assess the benefits as well as side effects of TRT, such as a suspected increase in CV event risk [12], prostate cancer or metabolic syndrome [13].

For this review, the terms 'functional hypogonadism' and 'testosterone deficiency' will be used interchangeably with 'late-onset hypogonadism' (currently considered an outdated term), depending on the name used by cited authors.

Material and methods

Publications from 1987 to August 2023 were searched via PubMed and GoogleScholar using the terms "testosterone", "hypogonadism", "LOH", "TRT", "cardiovascular diseases", "cardiovascular risk", "cardiovascular events", "Testosterone Trials", "metabolic syndrome", "muscle loss"; "diabetes", "prostate cancer", "psychology", "anabolic androgenic steroids", and "depression". Additional papers were found and studied through the references of those papers. Only articles in English were considered.

Testosterone and its functions in men's organism

Testosterone is the principal sex hormone produced and secreted by Leydig cells stimulated by luteinising hormone (LH). Its influence on the organism begins as early as in the first weeks of gestation when it starts conditioning the process of genital virilization, such as phallic enlargement, the development of seminal vesicles and prostate (however, these processes are influenced more by dihydrotestosterone than testosterone). Another organ influenced by testosterone is the brain, where during foetal growth, the aromatase converts testosterone to estradiol, causing masculinization and organisation of neural pathways characteristic of male behaviours [14].

Later on, in the third trimester, testosterone, along with the anti-Müllerian hormone (AMH), stimulates the development of sex by promot-

ing the degeneration of the Müllerian duct and growth of the Wolffian duct [15].

Before puberty, testosterone conditions the adrenarche, which manifests physically by developing adult body odour, axillary and pubic hair growth or an increase in testicular size. During puberty, masculine development stimulated by testosterone continues, resulting in the progressing appearance of tertiary sexual characteristics (for example, modification of skull shape, growth of facial hair, Adam's apple appearance, voice deepening) [16].

In adulthood, testosterone is necessary for maintaining spermatogenesis [17], muscle growth and inducing sexual activity [14]. It also seems to have a significant impact on motivation and ambition [18], as well as cognitive functions, which is especially noticeable in older men suffering from hypogonadism [19].

Finally, testosterone has a significant anti-inflammatory effect on multiple tissues. Low testosterone levels correlate with increased C-reactive protein (CRP), macrophage inflammatory proteins 1-α and 1-β and TNF-α, and many other pro-inflammatory cytokines and adipokines. This prolonged inflammation is one of the main reasons why testosterone's low levels may lead to metabolic syndrome, cardiovascular diseases, neurodegeneration and increased mortality risk [20], which our study will further discuss.

Cardiovascular diseases

Testosterone deficiency's influence on cardiovascular risk is a controversial and problematic topic. The available research lacks adequately powered randomized trials and does not provide sufficient longitudinal studies regarding TRT's safety in men with hypogonadism.

Meta-analyses considering the effect of endogenous T levels on CV risk have shown conflicting results. Corona et al. conducted a random effect meta-analysis using data from 37 observational studies published between 1988 and 2017 [21]. The analysis included 43,041 men at a mean age of 63.5 years, with a mean follow-up time of 333 weeks. The presented study showed that low T in ageing men is a marker of CV risk. However, the authors noted that the possible benefits of T treatment in reducing this risk should be examined in longer-term, specifically designed trials. Marriott et al. did not report the same results, who analyzed data on 20,180 men aged 64.9±3.3 years with a mean T concentration of 15.4±0.7 nmol/L measured using mass spectrometry [22]. This meta-analysis demonstrated no significant effect of a 5 nmol/L increase in T level on the risk of all-cause mortality or death from CV disease.

Although some studies conducted in the past have suggested that TRT may be associated with increased CV risk [23–26], several recently published meta-analyses have not supported such conclusions. Corona et al. gathered data from 15 pharmaco-epidemiological studies and 93 randomized placebo-controlled trials (RCT). They also found no indication of increased CV risk caused by correctly applied T therapy (TTh) with data from pharmaco-epidemiological studies suggesting that TTh reduces overall mortality and CV morbidity [27]. Fallara et al. analyzed data regarding 179,631 hypogonadal adult men (≥18 years old) and found that those treated with TTh had a lower all-cause mortality risk as compared to control groups without increased CV risk [28]. Hudson et al. also found no evidence that TTh increased short- or medium-term CV risk in men with hypogonadism [29]. This study involved RCTs, which included individual participant datasets (IPD), and investigated the effect of incorporating data from trials that did not provide IPD. Thirty-five primary studies were analyzed with a total of 5,601 participants at a mean age of 65. Finally, Ayele et al. conducted a systematic review analyzing the association between TRT and the risk of venous thromboembolism (VTE), which included 13 RCTs and a total of 5,050 men aged ≥18 years. The results suggested that TRT is not associated with an increased risk of VTE [30].

Several studies also analyzed the safety of TTh in patients with comorbidities. Mangolim et al. gathered data from 16 RCTs, including men with low T levels and obesity. Researchers found that in these men, TRT slightly improved lean body mass and LDL; however, its impact on CV events was unclear [31]. Another study conducted by Cannarella et al. aimed to assess the risk of TRT on cardiac function and angina in patients with low T levels coexisting with heart failure (HF) or coronary heart disease [32]. Seven RCTs, including 140 patients of NYHA class II and III,

were analyzed. Upon analysis, no effect of TRT on death and rehospitalization rates of patients with HF was found, and in patients with chronic angina, a significant delay in time to ischemia was observed.

Even though none of the meta-analyses described above suggested that TTh might be associated with increased CV risk when used as indicated, most concluded that further research is needed to confirm its safety.

On June 16, 2023, the results from the Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy Response in Hypogonadal Men (TRAVERSE) trial were presented at ENDO 2023. TRAVERSE trial is a randomized, double-blinded, placebo-controlled study conducted at 316 clinical trial sites in the United State [33]. A total of 5246 men between the ages of 45 and 80 were enrolled in the experiment and assigned in a 1:1 ratio to receive daily transdermal 1.62% testosterone gel or matching placebo gel. All participants had preexisting or a high risk of CV disease. Moreover, participants had to present at least one of the symptoms of hypogonadism, including decreased sexual desire or libido, decreased spontaneous erections, fatigue or decreased energy, low or depressed mood, loss of axillary or pubic body hair or decreased frequency of shaving, or hot flashes; and had to have two fasting serum testosterone levels of less than 300 ng/dL.

The primary safety end-point of the trial was the first occurrence of a major CV event (including death, nonfatal myocardial infarction, and nonfatal stroke). Upon analysis, researchers identified 182 patients (7.0%) in the testosterone group and 190 patients (7.3%) in the placebo group who suffered a major CV event (hazard ratio, 0.96; 95% confidence interval, 0.78 to 1.17; P<0.001 for noninferiority). After censoring the data on events that occurred more than 365 days after the last dose of TRT or placebo, a primary safety end-point event occurred in 154 patients (5.9%) in the testosterone group and 152 patients (5.8%) in the placebo group (hazard ratio, 1.02; 95% CI, 0.81 to 1.27; P<0.001 for noninferiority). It is also worth noting that the mean (±SD) duration of treatment and follow-up, respectively, were 21.7±14.1 and 33.0±12.1 months, and thus, there is still a need for longer-term studies with greater follow-up to ascertain the safety of TRT use [33].

TRAVERSE trial provides strong evidence regarding CV safety of adequately prescribed TRT; it is still essential to remember that this therapy may result in adverse effects. A higher incidence of nonfatal arrhythmias, atrial fibrillation and acute kidney injury has been reported among patients who received testosterone than among those who received placebo. Therefore, TRT should only be prescribed to middle-aged and older men with symptomatic androgen deficiency in whom testosterone is clinically indicated [33].

Diabetes

Testosterone, as an endogenous sex hormone, is an important factor in glucose metabolism and maintaining glucose homeostasis. However, it is not sure whether testosterone deficiency promotes the development of pre-diabetes and T2D or if it is the other way around [34]. There is no doubt a correlation that primary care doctors should be aware of, and all male patients with T2D should be screened for hypogonadism [35]. It is even more important when considering the results of the International Diabetes Federation. In 2019, 9.3% of the global population was estimated to have type 2 diabetes, and this percentage is expected to increase steeply in the following years. Moreover, half of the people with diabetes are not aware that they suffer from it [36].

A recent study found that among all age groups mean, testosterone levels were significantly lower in patients with diabetes than in corresponding non-diabetic groups. In addition, a longer duration of diabetes correlated with decreased testosterone levels [37]. Men in prediabetic states also have been found to have lower levels of testosterone than their healthy counterparts [38].

A study by Gouda et al. found that in non-obese (BMI below 30) men with T2D, one of the risk factors of testosterone deficiency is an elevated visceral adiposity index. This index could be used to predict testosterone deficiency in men without obesity with T2D [39]. In contrast, higher levels of testosterone have been associated with lower risks of developing T2D [5]. More so, increased testosterone is related to better outcomes of T2D development markers (better insulin sensitivity and lower levels of stimulated glucose) [38]. As a possible mechanism, Navar-

ro et al. showed that testosterone enhances the effect of glucagon-like peptide 1 (GLP-1) and the function of beta-cells [40].

TRT has been found to completely prevent the progression from prediabetes to type 2 diabetes in men with LOH [41]. Moreover, improvements in glycemia and lipid ratios were also observed [41, 42]. Additionally, the mortality rates were lower for patients with T2D whose testosterone levels were normal or who were on TRT compared with patients with T2D who suffered from testosterone deficiency [32].

Therefore, as TRT positively affects men with LOH, it might be used as a treatment for better T2D control and improvement in men's health.

Obesity, metabolic syndrome and muscle loss

There is strong evidence that low testosterone levels are associated with a higher prevalence of metabolic syndrome (MetS) in men of any age [9]. However, it has yet to be proven if the connection goes only through hyperinsulinism or if there is an independent association. A study with an 11-year follow-up has shown that even in men with normal BMI, there are significantly higher odds of developing MetS for men in the lower quartile of serum testosterone levels [44].

The exact role of testosterone and other sex hormones on human metabolism has not been clearly defined yet. However, the usually emphasised aspects are, among others, defective lipid uptake, lipolysis stimulation, and decreasing lipogenesis. In a 1999 study in which almost 400 males aged >20–85 were examined, there was a positive correlation found between age and BMI and fat mass (measured by impedance) and a negative correlation of age with levels of free testosterone and free insulin-like growth factor 1 (IGF-I) [45]. The role of testosterone in changes occurring during a lifetime may also be caused by its anabolic activity. Higher testosterone levels correlate with a lower lean mass loss in men over 65, as shown in a study that examined nearly 6000 men [46]. There was also a trial testing TRT in men with spinal cord injury and low testosterone serum levels that showed that after 12 months of TRT, there was a significant increase in the patients' lean tissue mass in comparison with the control group [47]. TRT has also proven effective in preventing muscle mass loss in HIV-infected patients [48]. The positive effect was most pronounced when intramuscular injections administered testosterone.

Prostate cancer

For a long time, scientists have not been able to conclude whether testosterone levels affect the development of cancer in men. The most likely and frequent possible cancer that depends on testosterone levels is prostate cancer.

In 2019, Kaipainen et al. conducted a study to test whether testosterone is a cancer growth factor through ligand-mediated androgen receptor activation. The study concluded that in addition to metabolism and transport of aldo-keto reductase family 1-member C3 (AKR1C3) – a hormone responsible for the conversion of androstenedione (AED) to testosterone – by tumour epithelium, testosterone can also be produced by components of the tumour microenvironment [49].

A meta-analysis conducted by Claps et al. in 2018 led to the conclusion that, depending on androgen deprivation therapy (ADT) intake and different clinical conditions, the association between circulating testosterone and prostate carcinoma (PC) prognosis varies [50]. For instance, in early PC, testosterone levels did not influence overall survival (OS). However, in advanced PC the prognosis and risk of death depended on the employment of ADT. Before ADT, higher testosterone levels correlated with a reduced risk of death, while during the said therapy, it was the low levels that reduced the risk of progression and death.

Also, in 2018, Walsh et al. conducted a retrospective initial cohort study of male veterans aged 40 to 89 years with laboratory-defined low testosterone levels between 2002 and 2011 and a recent prostate-specific antigen test. At first, the study found that only 313 out of the total number of men who were treated with testosterone had aggressive prostate cancer. However, upon adjusting for factors such as age, location, and other medical conditions, it was revealed that the incidence rate of aggressive prostate cancer was 0.57 per 1000 patients among untreated men and 0.58 per 1000 among treated men. Therefore, it was concluded

that there is no correlation between the cumulative dose or formula of testosterone and the development of prostate cancer [51].

Morales and Black described the case of a 71-year-old man who had previously undergone treatment for adenocarcinoma of the prostate gland. As a consequence the patient experienced a decrease in androgen levels and hypogonadism, as well as a decrease in libido, for which the patient decided to start testosterone replacement therapy. After half a year of testosterone treatment, the patient's prostate-specific antigen (PSA) increased, and therefore, he was advised to discontinue further testosterone treatment, which resulted in PSA's normalization. After the patient's death, caused possibly by a previously discovered hemorrhagic epidural mass and multiple pulmonary nodules, an autopsy was ordinated and revealed the prostate gland to be small with tumour cells histologically matching the ones found in the spine lesion and not originating from the prostate [52].

Based on such a small number of studies and articles, it cannot be claimed that testosterone affects the development of cancer in men, specifically prostate cancer. Many factors must be considered when conducting research, such as: age, comorbidities, place of work, and much more. Figuring this out is still a very relevant issue.

Osteoporosis

Bone demineralization is most commonly associated with estrogen deficiency (especially in the female population) – this mechanism is more frequently described in the literature and, therefore, better understood. Testosterone's influence on bone metabolism is relatively underrepresented in research but needs to be more important [53]. Osteoporosis is therefore often considered a "female" issue, with the male population presenting significantly lower prevalence and experiencing clinical manifestations much later (i.e. osteoporotic fractures occurring even ten years later in men's life than in women's), possibly because of a more gradual drop of testosterone levels. Despite that, morbidity and mortality of hip fractures are higher in men than in women [54], and only 10% of men receive proper treatment [55].

Traditional views suggest that testosterone deficiency in men has analogous effects on bone density as estrogen deficiency in women [56]. In a study from 1989, Stepan et al. showed a rapid decrease in bone density in castrated men, which led them to conclude that estrogen was the primary regulator of bone metabolism in women and testosterone in men. This theory was later modified over time by multiple studies, resulting in the currently accepted thesis that estrogens and testosterone play an important part in influencing men's bone metabolism [53].

Golds et al. mention in their review that due to the androgen receptors' presence in osteoblasts, osteocytes and osteoclasts, it is likely that testosterone has a direct influence on these cells, and therefore, on bone metabolism. However, based on a large Osteoporotic Fractures in Men Study (MrOS), the authors of this review point out that despite a clear correlation between hypogonadism and osteoporosis, the connection is possibly not based exclusively on free testosterone levels; the main factor influencing bone demineralization in men still seems to be low bioavailable estrogen (BioE2) and high sex hormone-binding globulin (SHBG). Free testosterone's effect on bone mineral density (BMD) seems to be nonsignificant, with only some (though not independent) effects on increased fracture risk [54].

Still, almost half of male osteoporosis cases have a secondary cause, one of the most frequently observed being hypogonadism [55]. Therefore, all cases of osteoporosis or idiopathic fragility fractures in older men should be investigated for possible secondary causes and treated accordingly.

Polycythemia

Polycythemia is an abnormally increased red blood cell mass. It is defined by the mass of red blood cells, which in men should be between 26 and 32 mL/kg [57]. That mass usually increases when hematocrit and haemoglobin values are above the norm, 51% and 185 g/L in men, respectively [58]. Secondary polycythemia is caused by chronic hypoxemia (obstructive sleep apnea, congestive heart failure) that stimulates the production of erythropoietin [59]. Testosterone also stimulates erythropoietin, increasing the haemoglobin

level and hematocrit [60]. Therefore, the low testosterone level in hypogonadism correlates with lower haemoglobin levels and lower haematocrit.. Introducing TRT can stop this decrease. However, in 4–40% of men, TRT may cause polycythemia and an increase of hematocrit, which, by increasing blood viscosity, may worsen already existing cardiovascular diseases [61].

At risk of developing erythrocytosis are especially older men treated with injections of testosterone preparations [62]. Injections have a higher chance of causing erythrocytosis than topical preparations [60].

Before starting TRT, the presence of conditions causing secondary polycythemia should be ruled out. Haematological assessment is needed to prevent hematocrit over 51% during TR, before starting the treatment, in 3–4 months, after a year of therapy and then annually. Moreover, to keep the hematocrit below the threshold of 52% dose adjustment or phlebotomy may be needed [63].

Impact of TRT on men's fertility

In men wanting to preserve fertility TRT is contraindicated [4]. TRT suppresses spermatogenesis, and that suppression may last even up to a year after the treatment is discontinued [64]. Instead of TRT, gonadotropin therapy is recommended for men with secondary hypogonadism who desire to preserve fertility. Functional secondary hypogonadism testicular function is intact and should respond well to stimulation with exogenous gonadotropin [4]. Rastrelli et al., in their meta-analysis, showed that in three-fourths of patients with hypogonadism, gonadotrophin therapy-induced sperm output [65]. hCG is the most common preparation used in gonadotrophin therapy [4]. In cases of organic secondary hypogonadism, a combination of hCG and FSH was shown to have a better outcome in restoring fertility [65]. Before starting TRT, informing the patient about possible side effects and considering their decision are crucial.

Pathopsychological effects

Psychological effects of high testosterone levels are a relatively new subject in the researchers' area of interest, with the main hypotheses mainly focused on an increase in aggressive and violent behaviours [66, 67], as well as the development of antisocial personality disorder (APD). The results of such studies still seem to be inconsistent. While there is evidence of a significant correlation of APD with high testosterone levels in saliva [68], other studies prove this relationship uncertain [69]. Some authors have even proved that higher testosterone levels have no significant link to aggression but rather to venturesomeness and adventure-seeking in men who are already diagnosed with personality disorders [70].

Yildirim et al. suggest that the original reason behind antisocial, sociopathic and psychopathic personalities might be high levels of foetal and circulating testosterone, which influence the maturation of mesolimbic dopaminergic circuitry responsible for emotional processing and empathy [71]. However, the same authors consider this aspect heavily modulated by other biological and psychosocial factors and conclude that higher testosterone levels cannot be considered a singular risk factor but rather a determinant that other elements must amplify to occur [71].

Another research suggests that cortisol is one of such biological factors capable of stimulating testosterone's influence on the subject's personality. In this study, Welker et al. point out that the positive correlation between testosterone and psychopathy only occurs in men with increased cortisol levels, with no such relationship observable in subjects with low cortisol. This theory's main limitation is, however, that it is impossible to decide whether high testosterone and cortisol are a cause, or a result of psychopathy [72].

In addition to those reports, Dreher et al. explored the subject of testosterone's stimulation of prosocial behaviours in men. They found out that the participants who had had testosterone injected were more prone to confrontational behaviours than those who had received a placebo. However, they also happened to be more generous, but only if such behaviour could enhance their economic and social status [73].

Similar conclusions might be drawn from the reports regarding anabolic androgenic steroids (AAS) use and their effects on men's neural function. AAS are known to pass through the blood-brain barrier. Since most common doses are supra-physiological (even 5–100 times great-

er than natural male production of testosterone), they are hypothesised to affect the central nervous system much more visibly than endogenous high levels of testosterone [74]. According to Hauger et al., such correlation is most commonly seen in AAS-dependent men, who showed more aggressive and violent behaviours than those who use AAS but have not developed a dependency.

It has also been pointed out that AAS abuse can often be linked with moodiness, anxiety, psychotic and manic episodes, as well as depression and suicide. However, it is still a topic of discussion whether such psychological complications are a result of AAS use or if they are independent comorbidities [75]. While overly high levels of testosterone induced by the abuse of AAS is suggested to contribute to the development of major depressive disorder, its naturally correct levels seem to be a protective factor against it. This correlation is most noticeable in men with hypogonadism. This group of patients shows a higher prevalence of anxiety disorders and major depressive disorder compared to men with correct levels of testosterone. A similar connection has been pointed out in patients who received anti-androgen treatment for prostate cancer [76, 77]. In an interesting study, Li et al. noticed that one of the enzymes responsible for testosterone's degradation is 3β- hydroxysteroid dehydrogenase (3β-HSD); they pointed out that rats infected with 3β-HSD-producing Escherichia coli manifested depressive behaviour with correlating lower serum and brain testosterone levels [77].

In contrast, Zarrouf et al. pointed out that TRT administration in hypogonadal men helped with diminishing the symptoms and improving the mood, which further supports the thesis of testosterone's protective qualities [78].

Conclusions

This review explores the most important aspects of testosterone's influence on the male body. Due to the wide range of possible consequences of testosterone's various levels, it is vital to consider the side effects when treating patients with both low and high serum testosterone. Some of the negative repercussions of abnormalities in testosterone levels are more directly dangerous than others. However, they all heavily influence the organism and should be analyzed and discussed with the patient. Low serum testosterone levels correlate with a higher risk of heart failure, In contrast, TRT may be a factor in reducing it, as well as having a protective effect on the heart and preventing early cardiovascular deaths. Similarly, a relationship between lower testosterone and a higher risk of metabolic disease and obesity has been noticed, where defective lipid uptake, lipolysis stimulation or decreasing lipogenesis are considered to be the main factors. Diabetes is another consequence of low testosterone, which is confirmed by tests run on men with both a prediabetic state and T2D. It is also possible that diabetes itself causes the reduction of testosterone levels, considering how men with a long history of diabetes seem to have considerably low levels of this hormone. A possible result is personality disorders, such as APD or psychopathy, as well as an increased risk of TRT-induced infertility and polycythemia.

Interestingly, high testosterone levels might also have a negative influence on a man's health. One of possible results are personality disorders, such as APD or psychopathy, as well as increased risk of TRT-induced infertility and polycythemia.

Considering how significant correct testosterone levels seem for maintaining both somatic and psychological health and well-being, it is imperative to continue research in this area.

Acknowledgements

Author contributions
D.S., K.C., Z.K., K.M., I.S. – conceptualization; Z.K., D.S., I.S., K.C., K.M. – writing (original draft preparation); I.P., Z.K. – writing (review & editing); I.P. – supervision.

Conflict of interest statement
The authors declare no conflict of interest.

Funding sources
There are no sources of funding to declare.

References

1. Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR; Baltimore Longitudinal Study of Aging. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab. 2001 Feb;86(2):724-31. doi: 10.1210/jcem.86.2.7219. PMID: 11158037.

2. Üçer O, Gümüş B. The treatment of late-onset hypogonadism. Turk J Urol. 2014 Sep;40(3):170-9. doi: 10.5152/tud.2013.97752. Epub 2014 Mar 24. PMID: 26328172; PMCID: PMC4548387.
3. Salter CA, Mulhall JP. Guideline of guidelines: testosterone therapy for testosterone deficiency. BJU Int. 2019 Nov;124(5):722-729. doi: 10.1111/bju.14899. Epub 2019 Sep 11. PMID: 31420972.
4. Corona G, Goulis DG, Huhtaniemi I, Zitzmann M, Toppari J, Forti G, Vanderschueren D, Wu FC. European Academy of Andrology (EAA) guidelines on investigation, treatment and monitoring of functional hypogonadism in males: Endorsing organization: European Society of Endocrinology. Andrology. 2020 Sep;8(5):970-987. doi: 10.1111/andr.12770. Epub 2020 Mar 20. PMID: 32026626.
5. Ding EL, Song Y, Malik VS, Liu S. Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. JAMA. 2006 Mar 15;295(11):1288-99. doi: 10.1001/jama.295.11.1288. PMID: 16537739.
6. Muraleedharan V, Marsh H, Kapoor D, Channer KS, Jones TH. Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes. Eur J Endocrinol. 2013 Oct 21;169(6):725-33. doi: 10.1530/EJE-13-0321. PMID: 23999642.
7. Boden WE, Miller MG, McBride R, Harvey C, Snabes MC, Schmidt J, McGovern ME, Fleg JL, Desvigne-Nickens P, Anderson T, Kashyap M, Probstfield JL. Testosterone concentrations and risk of cardiovascular events in androgen-deficient men with atherosclerotic cardiovascular disease. Am Heart J. 2020 Jun;224:65-76. doi: 10.1016/j.ahj.2020.03.016. Epub 2020 Mar 20. PMID: 32335402.
8. Lester JF, Mason MD. Cardiovascular effects of hormone therapy for prostate cancer. Drug Healthc Patient Saf. 2015 Jul 23;7:129-38. doi: 10.2147/ DHPS.S50549. PMID: 26229507; PMCID: PMC4516188.
9. Rodriguez A, Muller DC, Metter EJ, Maggio M, Harman SM, Blackman MR, Andres R. Aging, androgens, and the metabolic syndrome in a longitudinal study of aging. J Clin Endocrinol Metab. 2007 Sep;92(9):3568-72. doi: 10.1210/ jc.2006-2764. Epub 2007 Jun 26. PMID: 17595254.
10. Rodrigo Blaya, Leonardo Dalla Giacomassa Rocha Thomaz, Fernanda Guilhermano, Artur de Oliveira Paludo, Luiza Rhoden, Graziele Halmenschlager & Ernani Luis Rhoden (2016) Total testosterone levels are correlated to metabolic syndrome components, The Aging Male, 19:2, 85-89, doi: 10.3109/13685538.2016.1154523
11. Fantus RJ, Chang C, Platz EA, Bennett NE, Helfand BT, Brannigan RE, Halpern JA. Serum Total Testosterone and Premature Mortality Among Men in the USA. Eur Urol Open Sci. 2021 Jun 7;29:89-92. doi: 10.1016/j.euros.2021.05.008. PMID: 34337538; PMCID: PMC8317905.
12. Çatakoğlu AB, Kendirci M. Testosterone replacement therapy and cardiovascular events. Turk Kardiyol Dern Ars. 2017 Oct;45(7):664-672. doi: 10.5543/tkda.2017.00531. PMID: 28990951.
13. Ide V, Vanderschueren D, Antonio L. Treatment of Men with Central Hypogonadism: Alternatives for Testosterone Replacement Therapy. Int J Mol Sci. 2020 Dec 22;22(1):21. doi: 10.3390/ijms22010021. PMID: 33375030; PMCID: PMC7792781.
14. Mooradian AD, Morley JE, Korenman SG. Biological actions of androgens. Endocr Rev. 1987 Feb;8(1):1-28. doi: 10.1210/edrv-8-1-1. PMID: 3549275.
15. Xu HY, Zhang HX, Xiao Z, Qiao J, Li R. Regulation of anti-Müllerian hormone (AMH) in males and the associations of serum AMH with the disorders of male fertility. Asian J Androl. 2019 Mar-Apr;21(2):109-114. doi: 10.4103/aja.aja_83_18. PMID: 30381580; PMCID: PMC6413543.
16. Pinyerd B, Zipf WB. Puberty-timing is everything! J Pediatr Nurs. 2005 Apr;20(2):75-82. doi: 10.1016/j.pedn.2004.12.011. PMID: 15815567.
17. Smith LB, Walker WH. The regulation of spermatogenesis by androgens. Semin Cell Dev Biol. 2014 Jun;30:2-13. doi: 10.1016/j.semcdb.2014.02.012. Epub 2014 Mar 2. PMID: 24598768; PMCID: PMC4043871.
18. Sapienza P, Zingales L, Maestripieri D. Gender differences in financial risk aversion and career choices are affected by testosterone. Proc Natl Acad Sci U S A. 2009 Sep 8;106(36):15268-73. doi: 10.1073/pnas.0907352106. Epub 2009 Aug 24. PMID: 19706398; PMCID: PMC2741240.
19. Beauchet O. Testosterone and cognitive function: current clinical evidence of a relationship. Eur J Endocrinol. 2006 Dec;155(6):773-81. doi: 10.1530/eje.1.02306. PMID: 17132744.
20. Bianchi VE. The Anti-Inflammatory Effects of Testosterone. J Endocr Soc. 2018 Oct 22;3(1):91-107. doi: 10.1210/js.2018-00186. PMID: 30582096; PMCID: PMC6299269.
21. Corona G, Rastrelli G, Di Pasquale G, Sforza A, Mannucci E, Maggi M. Endogenous Testosterone Levels and Cardiovascular Risk: Meta-Analysis of Observational Studies. J Sex Med. 2018 Sep;15(9):1260-1271. doi: 10.1016/j.jsxm.2018.06.012. Epub 2018 Aug 23. PMID: 30145097.
22. Marriott RJ, Harse J, Murray K, Yeap BB. Systematic review and meta-analyses on associations of endogenous testosterone concentration with health outcomes in community-dwelling men. BMJ Open. 2021 Nov 2;11(11):e048013. doi: 10.1136/bmjopen-2020-048013. PMID: 34728442; PMCID: PMC8565564.
23. Basaria S, Coviello AD, Travison TG, Storer TW, Farwell WR, Jette AM, Eder R, Tennstedt S, Ulloor J, Zhang A, Choong K, Lakshman KM, Mazer NA, Miciek R, Krasnoff J, Elmi A, Knapp PE, Brooks B, Appleman E, Aggarwal S, Bhasin G, Hede-Brierley L, Bhatia A, Collins L, LeBrasseur N, Fiore LD, Bhasin S. Adverse events associated with testosterone administration. N Engl J Med. 2010 Jul 8;363(2):109-22. doi: 10.1056/NEJMoa1000485. Epub 2010 Jun 30. PMID: 20592293; PMCID: PMC3440621.
24. Xu L, Freeman G, Cowling BJ, Schooling CM. Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. BMC Med. 2013

Apr 18;11:108. doi: 10.1186/1741-7015-11-108. PMID: 23597181; PMCID: PMC3648456.
25. Vigen R, O'Donnell CI, Barón AE, Grunwald GK, Maddox TM, Bradley SM, Barqawi A, Woning G, Wierman ME, Plomondon ME, Rumsfeld JS, Ho PM. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. JAMA. 2013 Nov 6;310(17):1829-36. doi: 10.1001/jama.2013.280386. Erratum in: JAMA. 2014 Mar 5;311(9):967. PMID: 24193080.
26. Finkle WD, Greenland S, Ridgeway GK, Adams JL, Frasco MA, Cook MB, Fraumeni JF Jr, Hoover RN. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. PLoS One. 2014 Jan 29;9(1):e85805. doi: 10.1371/journal.pone.0085805. PMID: 24489673; PMCID: PMC3905977.
27. Corona G, Rastrelli G, Di Pasquale G, Sforza A, Mannucci E, Maggi M. Testosterone and Cardiovascular Risk: Meta-Analysis of Interventional Studies. J Sex Med. 2018 Jun;15(6):820-838. doi: 10.1016/j.jsxm.2018.04.641. PMID: 29803351.
28. Fallara G, Pozzi E, Belladelli F, Corsini C, Boeri L, Capogrosso P, Montorsi F, Salonia A. Cardiovascular Morbidity and Mortality in Men - Findings From a Meta-analysis on the Time-related Measure of Risk of Exogenous Testosterone. J Sex Med. 2022 Aug;19(8):1243-1254. doi: 10.1016/j.jsxm.2022.05.145. Epub 2022 Jun 23. PMID: 35753891.
29. Hudson J, Cruickshank M, Quinton R, Aucott L, Aceves-Martins M, Gillies K, Bhasin S, Snyder PJ, Ellenberg SS, Grossmann M, Travison TG, Gianatti EJ, van der Schouw YT, Emmelot-Vonk MH, Giltay EJ, Hackett G, Ramachandran S, Svartberg J, Hildreth KL, Groti Antonic K, Brock GB, Tenover JL, Tan HM, Kong CHC, Tan WS, Marks LS, Ross RJ, Schwartz RS, Manson P, Roberts S, Andersen MS, Magnussen LV, Hernández R, Oliver N, Wu F, Dhillo WS, Bhattacharya S, Brazzelli M, Jayasena CN. Adverse cardiovascular events and mortality in men during testosterone treatment: an individual patient and aggregate data meta-analysis. Lancet Healthy Longev. 2022 Jun;3(6):e381-e393. doi: 10.1016/S2666-7568(22)00096-4. PMID: 35711614; PMCID: PMC9184259.
30. Ayele HT, Brunetti VC, Renoux C, Tagalakis V, Filion KB. Testosterone replacement therapy and the risk of venous thromboembolism: A systematic review and meta-analysis of randomized controlled trials. Thromb Res. 2021 Mar;199:123-131. doi: 10.1016/j.thromres.2020.12.029. Epub 2021 Jan 6. PMID: 33486321.
31. Mangolim AS, Brito LAR, Nunes-Nogueira VDS. Effectiveness of testosterone replacement in men with obesity: a systematic review and meta-analysis. Eur J Endocrinol. 2021 Dec 3;186(1):123-135. doi: 10.1530/EJE-21-0473. PMID: 34738915.
32. Cannarella R, Barbagallo F, Crafa A, Mongioì LM, Aversa A, Greco E, Condorelli RA, LA Vignera S, Calogero AE. Testosterone replacement therapy in hypogonadal male patients with hypogonadism and heart failure: a meta-analysis of randomized controlled studies. Minerva Urol Nephrol. 2022 Aug;74(4):418-427. doi: 10.23736/S2724-6051.21.04307-X. Epub 2021 Mar 29. PMID: 33781026.
33. Lincoff AM, Bhasin S, Flevaris P, Mitchell LM, Basaria S, Boden WE, Cunningham GR, Granger CB, Khera M, Thompson IM Jr, Wang Q, Wolski K, Davey D, Kalahasti V, Khan N, Miller MG, Snabes MC, Chan A, Dubcenco E, Li X, Yi T, Huang B, Pencina KM, Travison TG, Nissen SE; TRAVERSE Study Investigators. Cardiovascular Safety of Testosterone-Replacement Therapy. N Engl J Med. 2023 Jul 13;389(2):107-117. doi: 10.1056/NEJMoa2215025. Epub 2023 Jun 16. PMID: 37326322.
34. Maresch CC, Stute DC, Alves MG, Oliveira PF, de Kretser DM, Linn T. Diabetes-induced hyperglycemia impairs male reproductive function: a systematic review. Hum Reprod Update. 2018 Jan 1;24(1):86-105.doi:10.1093/humupd/ dmx033. PMID: 29136166.
35. Corona G, Maggi M. Patients with testosterone deficiency syndrome and type 2 diabetes. Arch Esp Urol. 2013 Sep;66(7):711-22. PMID: 24047631.
36. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, Colagiuri S, Guariguata L, Motala AA, Ogurtsova K, Shaw JE, Bright D, Williams R; IDF Diabetes Atlas Committee. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract. 2019 Nov;157:107843. doi: 10.1016/j.diabres.2019.107843. Epub 2019 Sep 10. PMID: 31518657.
37. Kumari N, Khan A, Shaikh U, Lobes K, Kumar D, Suman F, Bhutto NS, Anees F, Shahid S, Rizwan A. Comparison of Testosterone Levels in Patients With and Without Type 2 Diabetes. Cureus. 2021 Jul 9;13(7):e16288.doi:10.7759/cureus. 16288. PMID: 34381648; PMCID: PMC8350217.
38. Leutner M, Matzhold C, Bellach L, Wohlschläger-Krenn E, Winker R, Nistler S, Endler G, Thurner S, Klimek P, Kautzky-Willer A. Increase in testosterone levels is related to a lower risk of conversion of prediabetes to manifest diabetes in prediabetic males. Wien Klin Wochenschr. 2022 Jan;134(1-2):1-6. doi: 10.1007/ s00508-021-01903-1. Epub 2021 Jul 5. PMID: 34223999; PMCID: PMC8813729.
39. Gouda SI, Aboelnaga MM, Elbeltagy AMG, Elbaz A. Testosterone deficiency in non-obese type 2 diabetic male patients. Arch Ital Urol Androl. 2022 Dec 27;94(4):464-469. doi: 10.4081/aiua.2022.4.464. PMID: 36576479.
40. Navarro G, Xu W, Jacobson DA, Wicksteed B, Allard C, Zhang G, De Gendt K, Kim SH, Wu H, Zhang H, Verhoeven G, Katzenellenbogen JA, Mauvais-Jarvis F. Extranuclear Actions of the Androgen Receptor Enhance Glucose-Stimulated Insulin Secretion in the Male. Cell Metab. 2016 May 10;23(5):837-51. doi: 10.1016/ j.cmet.2016.03.015. Epub 2016 Apr 28. PMID: 27133133; PMCID: PMC4864089.
41. Yassin A, Haider A, Haider KS, Caliber M, Doros G, Saad F, Garvey WT. Testosterone Therapy in Men With Hypogonadism Prevents Progression From Prediabetes to Type 2 Diabetes: Eight-Year Data From a

Registry Study. Diabetes Care. 2019 Jun;42(6):1104-1111. doi: 10.2337/dc18-2388. Epub 2019 Mar 12. PMID: 30862651.
42. Boyanov MA, Boneva Z, Christov VG. Testosterone supplementation in men with type 2 diabetes, visceral obesity and partial androgen deficiency. Aging Male. 2003 Mar;6(1):1-7. PMID: 12809074.
43. Hautanen A. Synthesis and regulation of sex hormone-binding globulin in obesity. Int J Obes Relat Metab Disord. 2000 Jun;24 Suppl 2:S64-70. doi: 10.1038/ sj.ijo.0801281. PMID: 10997612. Int J Obes Relat Metab Disord 2000; 24 Suppl 2: S64–70.
44. Laaksonen DE, Niskanen L, Punnonen K, Nyyssönen K, Tuomainen TP, Valkonen VP, Salonen R, Salonen JT. Testosterone and sex hormone-binding globulin predict the metabolic syndrome and diabetes in middle-aged men. Diabetes Care. 2004 May;27(5):1036-41. doi: 10.2337/diacare.27.5.1036. PMID: 15111517.
45. Vermeulen A, Goemaere S, Kaufman JM. Testosterone, body composition and aging. J Endocrinol Invest. 1999;22(5 Suppl):110-6. PMID: 10442580.
46. LeBlanc ES, Wang PY, Lee CG, Barrett-Connor E, Cauley JA, Hoffman AR, Laughlin GA, Marshall LM, Orwoll ES. Higher testosterone levels are associated with less loss of lean body mass in older men. J Clin Endocrinol Metab. 2011 Dec;96(12):3855-63. doi: 10.1210/jc.2011-0312. Epub 2011 Oct 5. PMID: 21976718; PMCID: PMC3232620.
47. Bauman WA, Cirnigliaro CM, La Fountaine MF, Jensen AM, Wecht JM, Kirshblum SC, Spungen AM. A small-scale clinical trial to determine the safety and efficacy of testosterone replacement therapy in hypogonadal men with spinal cord injury. Horm Metab Res. 2011 Jul;43(8):574-9. doi: 10.1055/s-0031-1280797. Epub 2011 Jun 29. PMID: 21717386.
48. Grinspoon S, Corcoran C, Askari H, Schoenfeld D, Wolf L, Burrows B, Walsh M, Hayden D, Parlman K, Anderson E, Basgoz N, Klibanski A. Effects of androgen administration in men with the AIDS wasting syndrome. A randomized, double-blind, placebo-controlled trial. Ann Intern Med. 1998 Jul 1;129(1):18-26. doi: 10.7326/0003-4819-129-1-199807010-00005. PMID: 9652995.
49. Kaipainen A, Zhang A, Gil da Costa RM, Lucas J, Marck B, Matsumoto AM, Morrissey C, True LD, Mostaghel EA, Nelson PS. Testosterone accumulation in prostate cancer cells is enhanced by facilitated diffusion. Prostate. 2019 Sep;79(13):1530-1542. doi: 10.1002/pros.23874. Epub 2019 Aug 2. PMID: 31376206;PMCID: PMC6783279.
50. Claps M, Petrelli F, Caffo O, Amoroso V, Roca E, Mosca A, Maines F, Barni S, Berruti A. Testosterone Levels and Prostate Cancer Prognosis: Systematic Review and Meta-analysis. Clin Genitourin Cancer. 2018 Jun;16(3):165-175.e2. doi: 10.1016/j.clgc.2018.01.005. Epub 2018 Feb 2. PMID: 29454638.
51. Walsh TJ, Shores MM, Krakauer CA, Forsberg CW, Fox AE, Moore KP, Korpak A, Heckbert SR, Zeliadt SB, Kinsey CE, Thompson ML, Smith NL, Matsumoto AM. Testosterone treatment and the risk of aggressive prostate cancer in men with low testosterone levels. PLoS One. 2018 Jun 22;13(6):e0199194. doi: 10.1371/journal.pone.0199194. PMID: 29933385; PMCID: PMC6014638.
52. Morales A, Black A. Testosterone deficiency syndrome and prostate cancer: illustrative annotations for a debate. Can Urol Assoc J. 2008 Feb;2(1):52-4. doi: 10.5489/cuaj.528. PMID: 18542732; PMCID: PMC2422889.
53. Khosla S, Monroe DG. Regulation of Bone Metabolism by Sex Steroids. Cold Spring Harb Perspect Med. 2018 Jan 2;8(1):a031211. doi: 10.1101/cshperspect.a031211. PMID: 28710257; PMCID: PMC5749141.
54. Golds G, Houdek D, Arnason T. Male Hypogonadism and Osteoporosis: The Effects, Clinical Consequences, and Treatment of Testosterone Deficiency in Bone Health. Int J Endocrinol. 2017;2017:4602129. doi: 10.1155/2017/4602129. Epub 2017 Mar 16. PMID: 28408926; PMCID: PMC5376477.
55. Bandeira L, Silva BC, Bilezikian JP. Male osteoporosis. Arch Endocrinol Metab. 2022 Nov 11;66(5):739-747. doi: 10.20945/2359-3997000000563. PMID: 36382763; PMCID: PMC10118818.
56. Stěpán JJ, Lachman M, Zvěrina J, Pacovský V, Baylink DJ. Castrated men exhibit bone loss: effect of calcitonin treatment on biochemical indices of bone remodeling. J Clin Endocrinol Metab. 1989 Sep;69(3):523-7. doi: 10.1210/jcem-69-3-523. PMID: 2788171.
57. Hocking WG, Golde DW. Polycythemia: evaluation and management. Blood Rev. 1989 Mar;3(1):59-65. doi: 10.1016/0268-960x(89)90026-x. PMID: 2650777.
58. Randi ML, Bertozzi I, Cosi E, Santarossa C, Peroni E, Fabris F. Idiopathic erythrocytosis: a study of a large cohort with a long follow-up. Ann Hematol. 2016 Jan;95(2):233-7. doi: 10.1007/s00277-015-2548-z. Epub 2015 Nov 7. PMID: 26547864.
59. Haider MZ, Anwer F. Secondary Polycythemia. 2023 May 8. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan–. PMID: 32965904.
60. Bachman E, Travison TG, Basaria S, Davda MN, Guo W, Li M, Connor Westfall J, Bae H, Gordeuk V, Bhasin S. Testosterone induces erythrocytosis via increased erythropoietin and suppressed hepcidin: evidence for a new erythropoietin/hemoglobin set point. J Gerontol A Biol Sci Med Sci. 2014 Jun;69(6):725-35. doi: 10.1093/gerona/glt154. Epub 2013 Oct 24. PMID: 24158761; PMCID: PMC4022090.
61. Levcikova M, Breza J Jr, Luha J, Dubravicky J, Kovacova E, Fillo J. Testosterone replacement therapy (TRT) and its effect on bone marrow. How serious is it and is there a true polyglobulia? Bratisl Lek Listy. 2017;118(11):654-657. doi: 10.4149/BLL_2017_124. PMID: 29216720.
62. Wang C, Nieschlag E, Swerdloff R, Behre HM, Hellstrom WJ, Gooren LJ, Kaufman JM, Legros JJ, Lunenfeld B, Morales A, Morley JE, Schulman C, Thompson IM, Weidner W, Wu FC. Investigation, treatment and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA and ASA recommendations. Eur J Endocrinol. 2008 Nov;159(5):507-14. doi: 10.1530/EJE-08-0601. PMID: 18955511; PMCID: PMC2754376.

63. Bassil N, Alkaade S, Morley JE. The benefits and risks of testosterone replacement therapy: a review. Ther Clin Risk Manag. 2009 Jun;5(3):427-48. doi: 10.2147/tcrm.s3025. Epub 2009 Jun 22. PMID: 19707253; PMCID: PMC2701485.
64. Christou MA, Christou PA, Markozannes G, Tsatsoulis A, Mastorakos G, Tigas S. Effects of Anabolic Androgenic Steroids on the Reproductive System of Athletes and Recreational Users: A Systematic Review and Meta-Analysis. Sports Med. 2017 Sep;47(9):1869-1883. doi: 10.1007/s40279-017-0709-z. PMID: 28258581.
65. Rastrelli G, Corona G, Mannucci E, Maggi M. Factors affecting spermatogenesis upon gonadotropin-replacement therapy: a meta-analytic study. Andrology. 2014 Nov;2(6):794-808. doi: 10.1111/andr.262. Epub 2014 Oct 1. PMID: 25271205.
66. James M. Dabbs, Timothy S. Carr, Robert L. Frady, Jasmin K. Riad, Testosterone, crime, and misbehavior among 692 male prison inmates, Personality and Individual Differences, Volume 18, Issue 5, 1995, Pages 627-633, ISSN 0191-8869, https://doi.org/10.1016/0191-8869(94)00177-T.
67. Dabbs JM Jr, Frady RL, Carr TS, Besch NF. Saliva testosterone and criminal violence in young adult prison inmates. Psychosom Med. 1987 Mar- Apr;49(2):174-82. doi: 10.1097/00006842-198703000-00007. PMID: 3575604.
68. Anu S Aromäki, Ralf E Lindman, C.J.Peter Eriksson, Testosterone, sexuality and antisocial personality in rapists and child molesters: a pilot study, Psychiatry Research, Volume 110, Issue 3, 2002, Pages 239-247, ISSN 0165-1781, https://doi.org/10.1016/S0165-1781(02)00109-9.
69. House, S.J., Laan, J.M., Molden, R.K., Ritchie, J.C. and Stowe, Z.N. (2017), Preliminary Study of Testosterone and Empathy in Determining Recidivism and Antisocial Behavior. J Forensic Sci, 62: 1360-1365. https://doi.org/ 10.1111/1556-4029.13469
70. Coccaro EF, Beresford B, Minar P, Kaskow J, Geracioti T. CSF testosterone: relationship to aggression, impulsivity, and venturesomeness in adult males with personality disorder. J Psychiatr Res. 2007 Sep;41(6):488-92. doi: 10.1016/j.jpsychires.2006.04.009. PMID: 16765987.
71. Yildirim BO, Derksen JJ. A review on the relationship between testosterone and life-course persistent antisocial behavior. Psychiatry Res. 2012 Dec 30;200(2-3):984-1010. doi: 10.1016/j.psychres.2012.07.044. Epub 2012 Aug 25. PMID: 22925371.
72. Welker KM, Lozoya E, Campbell JA, Neumann CS, Carré JM. Testosterone, cortisol, and psychopathic traits in men and women. Physiol Behav. 2014 Apr 22;129:230-6. doi: 10.1016/j.physbeh.2014.02.057. Epub 2014 Mar 11. PMID: 24631306.
73. Dreher JC, Dunne S, Pazderska A, Frodl T, Nolan JJ, O'Doherty JP. Testosterone causes both prosocial and antisocial status-enhancing behaviors in human males. Proc Natl Acad Sci U S A. 2016 Oct 11;113(41):11633-11638. doi: 10.1073/pnas.1608085113. Epub 2016 Sep 26. PMID: 27671627; PMCID: PMC5068300.
74. Lisa E. Hauger, Ingrid A. Havnes, Marie L. Jørstad, Astrid Bjørnebekk, Anabolic androgenic steroids, antisocial personality traits, aggression and violence, Drug and Alcohol Dependence, Volume 221, 2021, 108604, ISSN 0376-8716, https://doi.org/10.1016/j.drugalcdep.2021.108604
75. Piacentino D, Kotzalidis GD, Del Casale A, Aromatario MR, Pomara C, Girardi P, Sani G. Anabolic-androgenic steroid use and psychopathology in athletes. A systematic review. Curr Neuropharmacol. 2015 Jan;13(1):101-21. doi: 10.2174/1570159X13666141210222725. PMID: 26074746; PMCID: PMC4462035.
76. McHenry J, Carrier N, Hull E, Kabbaj M. Sex differences in anxiety and depression: role of testosterone. Front Neuroendocrinol. 2014 Jan;35(1):42-57. doi: 10.1016/j.yfrne.2013.09.001. Epub 2013 Sep 24. PMID: 24076484; PMCID: PMC3946856.
77. Li D, Liu R, Wang M, Peng R, Fu S, Fu A, Le J, Yao Q, Yuan T, Chi H, Mu X, Sun T, Liu H, Yan P, Wang S, Cheng S, Deng Z, Liu Z, Wang G, Li Y, Liu T. 3β- Hydroxysteroid dehydrogenase expressed by gut microbes degrades testosterone and is linked to depression in males. Cell Host Microbe. 2022 Mar 9;30(3):329-339.e5. doi: 10.1016/j.chom.2022.01.001. Epub 2022 Feb 1. PMID: 35108497.
78. Zarrouf FA, Artz S, Griffith J, Sirbu C, Kommor M. Testosterone and depression: systematic review and meta-analysis. J Psychiatr Pract. 2009 Jul;15(4):289-305. doi: 10.1097/01.pra.0000358315.88931.fc. PMID: 19625884.