



## Testosterone Replacement in Middle-Aged Men: A Review

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### ABSTRACT

Testosterone deficiency encompasses clinically low serum testosterone levels accompanied by signs and symptoms. This testosterone decline is expected in older men and begins in middle age (40 to 64 years) and is commonly treated through Testosterone Replacement Therapy (TRT). This review aims to look at the mechanisms of TRT, physiological and societal motivations to seek TRT, ethical and medical considerations behind its use, and future research directions. From the review of numerous papers looking at testosterone therapy in middle-aged men, various mechanisms for the delivery of testosterone were isolated, each with sufficient risks and benefits. Of all the mechanisms looked at, buccal testosterone and implants had more benefits than others in patient adherence and normal circadian variations in serum testosterone, unlike Intramuscular testosterone. Both physiological and societal changes in middle-aged men cause them to seek therapy. Some of these physiological changes include sarcopenia, reduction in bone mineral density, depressive mood symptoms, reduced libido, and erectile dysfunction. Societal changes, which also influence treatment-seeking, include feelings of "lost masculinity" associated with loss of strength and virility with old age. This societal pressure can lead to a desire to maintain youthful vigor, a significant motivator for seeking TRT. Due to substantial societal and media changes, TRT use in the United States has tripled between 2001 and 2011, raising concerns that many individuals may be receiving treatment without being appropriately informed on the risks and benefits and without clear clinical indications. Although extensive research is available in this field, there remain unanswered questions regarding the effects on non-communicable diseases like cardiovascular disease and cancers. While prostate cancer, in particular, is not related to TRT use, further research is needed to prove the relationship. Additionally, there is untapped potential for TRT beyond the scope of hypogonadism, but researchers have yet to explore these areas of benefit.

**Key words:** Testosterone, Testosterone replacement therapy, Hormone replacement, Middle-aged men, Testosterone decline, Testosterone deficiency, Intramuscular testosterone.

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### INTRODUCTION

Testosterone deficiency refers to the condition where there is a low level of serum testosterone, accompanied by consistent symptoms or signs. It could occur in both men and women but is a relatively common phenomenon correlating

with an increase in age in physiological males [1]. This condition also referred to as late-onset hypogonadism or andropause, manifests through easily recognizable symptoms including but not limited to decreased libido, increased adiposity, muscle weakness, erectile dysfunction, and decreased vitality [2]. Testosterone levels have been known to decline gradually with age, more so in men with comorbid conditions like obesity and comorbid conditions (chronic liver disease, type 2 diabetes mellitus). Although age-related testosterone decline is not an indication for testosterone replacement due to a scarcity of data related to the efficacy and risks in older men, the majority of testosterone prescriptions are still written for men aged between 40 and 64 years [3]. This surge in testosterone treatment in older men undergoing a biological process is due in part to the current era of medicalization of masculinity, where media has portrayed the natural phenomenon of aging as a disease that can and should be prevented, prompting men of older age worrying about having 'lost masculinity' due to naturally declining testosterone to seek pharmaceutical remedies in the form of hormone replacement [4]. This paper reviews relevant studies on the benefits and risks of testosterone replacement therapy in middle-aged men, the selection of suitable candidates for therapy, current controversies in the medical community regarding hormone replacement, and knowledge gaps for future research in men's health.

#### MECHANISMS OF TESTOSTERONE REPLACEMENT

Ever since the conception of modern androgen therapy in the Mid-30s, there have been a variety of improvements and modifications made to the pharmacokinetics and pharmacodynamics of testosterone and its analogs [5]. Different routes of administration have been formulated, with each of them having its pros and drawbacks; these include but are not limited to injectable testosterone, transdermal testosterone, and oral testosterone [6].

#### Intramuscular injectable testosterone

This preparation is one of the oldest and most reliable forms of TRT, established in the 1950s. When testosterone is injected in its naturally occurring state, it has a short half-life, which is estimated to be around 10 minutes which doesn't yield much therapeutic benefit. However, modern formulations esterify its 17 $\beta$  carbon

hence increasing the solubility of testosterone in oil and allowing for a slower release when injected into the muscle. In addition, the esterified testosterone is not biologically active until the ester group is cleaved off, consequently extending its half-life [7]. There are several approved preparations of injectable Testosterone (T) for treatment, including Testosterone Cypionate (TC), Testosterone Enanthate (TE), Testosterone Propionate (TP), and Testosterone Undecanoate (TU). The absorption kinetics of these preparations differ based on several factors, including the position of the esterified fatty acids to the 17 $\beta$  position of testosterone, the oily vehicle used, the injection site, and the injection volume. Intramuscular formulations have been shown to increase muscle strength and fat-free body mass in both elderly and middle-aged men, which makes it a better alternative to other formulations like transdermal [8]. A major drawback for patients is the pain and inconvenience experienced with taking each dose. Other documented side effects include shortness of breath and an uncontrollable urge to cough but these are rare and have been linked to pulmonary oil embolism [9]. It is worth noting that Testosterone Undecanoate (TU), though extremely rare, has been associated with POME that can sometimes require epinephrine for treatment [10].

#### Transdermal testosterone-Patch

Transdermal testosterone is another form of TRT that involves applying testosterone gel or patch to the skin daily. The first transdermal formulations of testosterone were poorly accepted as they were made to be used on the scrotal skin. Further research led to the development of non-scrotal transdermal patches, which are now available in 2 or 4 mg /d formulations [11,12]. Transdermal patches are non-invasive, easy to apply, and have a quick reversal after removal, with good adhering to simulation of normal circadian rhythm unlike other testosterone preparations [13]. Compare the effectiveness of transdermal versus Intramuscular (IM) formulations in treating male hypogonadism. The study found that despite both formulations maintaining sexual function and mood at normal physiological levels, the transdermal system produced circadian variations within normal

physiological ranges, while the injections resulted in supraphysiological testosterone levels for several days after each injection. Hence, the transdermal system was found to be more effective in producing normal morning sex hormone levels (77%-100%) compared to the injections (19%-84%). Noticeable drawbacks of testosterone patches included skin reactions that were observed in 60% of Testosterone Transdermal System (TTD) patients, leading to discontinuation in 9%. TTD also had a smaller influence on hematocrit elevation than Intramuscular (IM) testosterone (43.8% elevation seen in IM vs. 15.4% for TTD). TTD achieved hypogonadal concentrations within 24 hours of patch removal with a half-life of 1.3 hours which is lower than that of IM making frequent dosage in TTD a noticeable disadvantage among patients [14].

#### Nasal testosterone

In 2014 nasal testosterone was approved for Testosterone Replacement Therapy (TRT) by the US FDA with the trade name Natesto™. It is available in 15 European countries and is administered via ametered-dose pump applicator [15]. The recommended dosage is two pumps three times daily, totaling 33 mg daily. Two open-label phase III trials in the USA [16] and Canada [17] included 306 hypogonadal men treated for 90 days. Ninety percent achieved serum Testosterone concentrations within the normal range (average 421 ng/dL), with normal DHT and estradiol levels. Improved erectile function, mood, body composition, and bone mineral density were observed. The treatment was well-tolerated, but 2.9% was discontinued due to drug-related adverse events, including increased prostate-specific antigen levels, headache, and nasal-related issues which included rhinorrhea, nosebleeds, nasal discomfort, upper respiratory tract infections, sinusitis, bronchitis and nasal scab. A reduction in the dosage of nasal gel to two times daily in hypogonadal men did not reduce LH and FSH concentrations below the normal range and failed to maintain sperm production. Comparing nasal testosterone to topical gel revealed a 15% improvement in symptoms from baseline to day 90 with Testosterone Nasal Gel (TNG), indicating its effectiveness in addressing testosterone deficiency symptoms. Compared to previous topical therapy, TNG scored higher in effectiveness (+20%), convenience (+30%),

and global satisfaction (+3%) [18]. Patients appreciated TNG for its ease of use, convenience, and travel friendliness. Overall, 67.2% preferred TNG over topical therapy, and 59% sought a prescription to continue TNG treatment, emphasizing high patient satisfaction and preference for TNG.

#### Gel

These formulations come with a United States Food and Drug Administration (FDA)-issued box warning due to concerns about potential transfer to others, except for particular gel-formulations with a hands-free cap applicator (2% Testosterone gel) that lack the warning [19]. Gels offer ease of application, reduced skin irritation, and more consistent serum testosterone levels than intramuscular preparations. Different concentrations of transdermal testosterone formulations are available, including 1%, 1.62%, and 2% with various dosage forms [20]. (2000) studied the pharmacokinetics of 1% testosterone gel, which showed a compliance rate of approximately 90% [21]. The only widely reported disadvantage of the gel form is the risk of transfer to another individual through contact which can be easily mitigated through proper precautions like washing hands after application and avoiding direct contact of areas of application to unknowing individuals. Transdermal preparations provide flexible dosing and rapid elimination upon removal, making them preferred for treating side effects. They have been widely used in hypogonadal men, including those with Late-Onset Hypogonadism (LOH), and have positive effects on sexual function [22].

#### Oral Testosterone

Oral testosterone is a less commonly used form of TRT that involves taking testosterone pills daily. However, it is not commonly used due to an increased risk of liver damage [23]. The rationale for using oral testosterone is that it provides a convenient method of delivery without the need for injections or skin contact. However, the risk of liver damage may limit its use, and other forms of TRT may be more effective and safer [24].

#### Buccal Testosterone

Buccal testosterone became available for use in the early 2000s through a twice-daily mucoadhesive capsule applied to the gingivae [25]. Hypo gonadal men to observe the efficacy and safety of buccal testosterone; it showed

testosterone levels peaking within 30 minutes and returning to baseline after 4-6 hours [26]. Another pharmacological study done also showed that buccal testosterone declined to subtherapeutic levels significantly faster than injectable testosterone, and reached therapeutic levels faster than sublingual testosterone. During clinical trials, buccal testosterone was found to be well-tolerated for up to a year [27]. However, only a small number of men with hypogonadism were involved in the trials (1998), so the effectiveness of buccal formulations in treating symptoms of testosterone deficiency was not determined. Reported experiencing gum-related side effects like irritation, inflammation, gingivitis, or dysgeusia [28]. The homogenates were diluted with distilled water in ratio 1:9. An aliquot of 0.2 ml of the diluted sample was added to the 2.5 ml of 0.05M carbonate buffer, pH 10.2 to equilibrate in the spectrophotometer cuvette and the reaction started by adding 0.3ml freshly prepared 0.03 mM epinephrine to the mixture which was quickly mixed by inversion. The reference cuvette contained 2.5ml of carbonate buffer, 0.3ml of substrate (adrenaline) and 0.2ml of distilled water [29].

The increase in absorbance at 480 nm was monitored every 30 sec for 150 sec [30, 31].

#### SCIENTIFIC BASIS AND RATIONALE FOR TRT USE

##### Review of the Physiological Changes in Middle-Aged Men

Evidence suggests that aging results in a gradual decline in androgen levels, such as Testosterone (T) and Dehydroepiandrosterone (DHEA), which begin at ages 35 to 40 and continue throughout life [32, 33,34]. However, it is unclear whether this decrease is a natural part of the aging process or if other factors, such as diseases or changes in lifestyle, influence it [35, 36, 37]. Evidence supports that the attrition of testosterone-producing Leydig cells and DHEA-secreting cells in the zona reticularis of the adrenals is the underlying cause of the decline in androgen hormones in middle-aged and elderly men [38, 39]. However, inconsistent data surrounds changes in estradiol levels. An increase in sex hormone-binding globulin levels is also noticed in aging men, leading to more significant decreases in calculated free testosterone levels than total testosterone. It is

essential to understand the natural history and determinants of these changes [40, 41].

#### CRITICAL ASSESSMENT OF SCIENTIFIC (MEDICAL) EVIDENCE SUPPORTING HRT EFFECTIVENESS

Testosterone (T) treatment has garnered significant attention for its potential beneficial effects, particularly in men exhibiting symptoms of testosterone deficiency and repeatedly low serum testosterone concentrations. Evidence from testosterone therapy studies targeting age-related conditions such as Body composition, depressive mood, and sexual dysfunction is summarized as follows:

##### Body composition

As men age, they become more susceptible to fractures and the development of age-related sarcopenia, a medical condition characterized by a progressive loss of muscle mass. The prevalence of moderate to severe sarcopenia in men over 60 is significant, underscoring the substantial impact of aging on musculoskeletal health. Testosterone (T) therapy has emerged as a potential intervention to mitigate these effects [42,43,44,45].Improvements in bone mineral density, increased fat-free mass, and reductions in body fat have been observed with testosterone treatment, with more pronounced results in the elderly [46]. The beneficial effects of testosterone supplementation on body composition, including reducing body fat and waist circumference and improving insulin resistance, lipid profile, blood pressure, and lean body mass, have been confirmed by recent large-scale studies [47, 48, 49].

##### Mood

A few studies have investigated the impact of Testosterone (T) on mood, with one being a double-blind placebo-controlled trial involving HIV positive patients with low testosterone and depressive symptoms, men aged 30-65 years diagnosed with major depressive disorder with low testosterone [50], and dysthymic men with low testosterone. Results from these studies have suggested that testosterone supplementation has a positive effect with participants having self-reported increase in mood. On men with selective serotonin reuptake inhibitor-resistant depression failed to demonstrate any significant improvement in depressive symptoms[51].

A recent meta-analysis has confirmed that testosterone administration has favorable effects on depressive symptoms, with a dose-response relationship established [52]. Despite these findings, it is essential to note that testosterone supplementation is not currently recommended as an additional treatment for major depressive disorders in men, as per clinical practice guidelines on testosterone therapy in hypogonadal men or depression treatment guidelines [53].

### **Sexual function**

Sexual dysfunction, including reduced libido and erectile dysfunction, is prevalent among aging men, affecting up to 77.5% of those over 75 years old [54]. While some studies have not supported Testosterone (T) supplementation in older men with sexual dysfunction and low testosterone levels, in which they concluded that more studies need to be done with higher doses of androgen and with different routes of administrations [55], most research reports positive effects [56,57,58]. Several research studies have demonstrated the advantageous effects of testosterone treatment on sexual function. These benefits include enhancements in sexual desire, orgasm, and intercourse satisfaction [59, 60, 61]. Further analyses of the testosterone Trials, in which included 470 older men, found that testosterone supplementation resulted in significant improvements in sexual activity and desire [62]. Independent meta-analyses further confirmed the positive effects of testosterone supplementation on sexual function in men, including improvements in erectile function, libido, and overall quality of life [63, 64]. Despite potential publication bias, these analyses highlighted testosterone's consistent and robust positive effect on sexual health. In summary, sexual dysfunction has a high correlation with an increase in age in men. However, while early studies were inconclusive, subsequent research consistently demonstrates improvements in sexual desire, orgasm, and satisfaction with testosterone treatment.

## **SOCIETAL AND ETHICAL CONSIDERATIONS**

### **Examination of the Societal Expectations Influencing Patient Decisions**

Societal expectations and perceptions surrounding Testosterone Replacement Therapy (TRT) in middle-aged men are influenced by a

variety of factors, including cultural norms, media representation, and evolving attitudes toward aging and masculinity. These expectations and perceptions can significantly impact how individuals consider and approach Testosterone Replacement Therapy (TRT) [65, 66]. Societal norms often link masculinity with attributes like strength, virility, and sexual prowess [67]. There is usually a link between virility and sexual prowess in a man's identity [68, 69]. TRT, with its potential benefits in terms of libido and sexual function, may be perceived as a way to align with these traditional expectations. Aging is sometimes perceived as a decline in these attributes, leading to the desire for interventions like TRT to maintain a sense of youthful vigor. This is further influenced by the media that often portrays idealized images of masculinity that have impacted greatly on societal expectations [70]. Pharmaceutical advertisements for TRT may reinforce the idea that vitality and masculinity are closely linked to hormone levels [71]. Societal expectations regarding physical fitness and appearance can impact the perception of masculinity. TRT may be considered a tool to enhance muscle mass, reduce body fat, and maintain a more youthful physical appearance. In as much as age-related decline in circulating levels of hormones, particularly testosterone, in middle-aged men can be viewed as a symptom of aging, one of its potential mechanisms, cultural expectations regarding aging and masculinity can influence the acceptance or resistance to TRT. Different cultures hold distinct attitudes toward aging and masculinity [72]. In some societies, there may be a greater emphasis on preserving traditional masculine attributes, while in others; a more holistic view of aging may be embraced. In cultures where elders are revered, there may be less pressure to conform to youthful ideals. Hence the variation in popularity of TRT around the world. In professional settings, especially those with a strong emphasis on productivity and competitiveness there may be pressure on older individuals, particularly men, to maintain peak performance [73]. Middle-aged men may feel pressure to maintain high energy levels and cognitive function. TRT could be considered to enhance overall work performance and competitiveness in areas like the military and organized sports. Societal expectations regarding age and masculinity can have psychological implications. The fear of not meeting these

expectations may contribute to the consideration of TRT as a way to boost confidence and psychological well-being [74]. Understanding these societal expectations and perceptions is essential for healthcare professionals and policymakers when considering the ethical implications and guidelines for TRT. It highlights the importance of fostering informed decision-making, ensuring that individuals are aware of the potential risks and benefits, and addressing societal pressures that may influence choices related to hormone replacement therapy. Additionally, it emphasizes the need for open conversations about aging, masculinity, and the diverse ways individuals experience and navigate these aspects of life [75].

#### **ETHICAL CONSIDERATIONS SURROUNDING THE MEDICALIZATION OF AGING**

The medicalization of aging, particularly concerning Testosterone Replacement Therapy (TRT) in middle-aged men, raises ethical considerations that should be carefully addressed [76,77]. Some specific ethical considerations related to the medicalization of aging through TRT include;

##### **Informed Consent and Shared Decision-Making:**

Ethical practice necessitates open communication and a thorough discussion between healthcare providers and middle-aged individuals about the potential benefits, risks, and alternatives to TRT. Informed consent is crucial to ensure that individuals understand the implications and make decisions aligned with their values and preferences [78].

##### **Normalization of Aging and Testosterone Levels:**

Promoting a narrative that values and respects the diversity of aging experiences is important as it is normal for different individuals to experience aging in different ways [79]. Ethical concerns arise if TRT contributes to the normalization of a specific level of testosterone as "normal" for aging men, potentially pathologizing natural variations. It's important to consider the diversity of aging experiences and avoid overgeneralizing normative values.

##### **Appropriate Clinical Indications:**

The appropriate clinical indications for Testosterone Replacement Therapy (TRT) in middle-aged men involve careful consideration of medical and ethical factors. Ethical considerations

include ensuring that TRT is prescribed based on legitimate clinical indications rather than social or aesthetic reasons. Since the early 2000s, TRT has been gaining popularity and hundreds of testosterone clinics emerged to capitalize on this trend [80, 81]. From 2001 to 2011, the use of testosterone in the United States tripled, and hundreds of testosterone clinics emerged to capitalize on this trend [82]. During the same period, total testosterone sales increased 12-fold globally. These for-profit clinics represented the original men's health clinics and provided patients with various forms of testosterone replacement therapy, often without a clear indication [83]. These centers generally only offer patients injection therapy, which provides patients with a sudden, feel-good rush, making the next injection more appealing. The main concern with centers that monetize testosterone therapy is whether they accurately make a diagnosis, listen to all of a patient's symptoms, and properly tailor treatment regimens. Rather than assessing symptoms, these clinics may be more inclined to market testosterone replacement due to financial incentives [84]. This poses a serious ethical dilemma. A thorough evaluation of the symptomatology and presentations that are significant for low testosterone levels should guide the decision to prescribe TRT. Emphasis should be placed on scientific evidence in guiding decision-making. It is also important that ethical considerations include the exclusion of reversible or treatable causes of symptoms before initiating TRT. Providers should conduct a thorough evaluation to rule out secondary causes, such as medication side effects, lifestyle factors, or underlying medical conditions before initiation of TRT.

##### **Long-Term Health Implications:**

Patients receiving testosterone therapy need close monitoring due to its associated risks; however, most of the emerging clinics lack the follow-up protocol typically offered in a traditional physician's office [85]. Ethical decision-making involves considering the potential long-term health implications of TRT. Providers should discuss the risks, including cardiovascular and prostate-related concerns, and ensure that individuals are aware of the potential impact on their overall health. While there is a compelling marketing drive for nontraditional men's clinics that merely administer testosterone therapy,

there is certainly a missed opportunity to evaluate men in further detail and discuss the prostate cancer risk or fertility implications of testosterone replacement [86]. By incorporating these ethical considerations into the decision-making process, healthcare providers can ensure that TRT is prescribed judiciously and in the best interest of the patient's health and well-being. Regular communication, ongoing monitoring, and a commitment to ethical principles are essential elements of providing responsible and patient-centered care.

#### **IMPACT ON HEALTHCARE RESOURCES AND DISTRIBUTION**

Testosterone replacement therapy has an impact on healthcare that can be described as multifaceted involving cost considerations, access disparities, and other broader issues in the healthcare system [87,88]. TRT involves ongoing costs for both the medications and the necessary monitoring, including laboratory tests [89]. The economic impact includes the expenses associated with the prescription of testosterone products, physician visits, and follow-up assessments [90]. The financial burden may fall on individuals, insurance providers, or public healthcare systems [91, 92]. This also brings up the issue of disparity in accessibility. The availability of TRT and the associated healthcare resources may vary across different regions and healthcare systems. There could be disparities in access, with certain populations facing challenges in obtaining TRT due to factors such as geographical location, socioeconomic status, or insurance coverage [93]. Another factor that may have a significant impact on the availability and accessibility of TRT is the distribution of a specialized workforce. The prescription and management of TRT often require specialized knowledge, typically from endocrinologists or urologists. The distribution of healthcare providers with expertise in TRT may influence access; potentially creating challenges in regions with a shortage of specialists [94, 95]. Unnecessary strain can be placed on healthcare resources due to the overutilization of TRT, including inappropriate prescribing without clear clinical indications. Laboratory tests, appointments, treatments and regular monitoring, including follow-up appointments may contribute to increased costs and could

divert resources away from interventions with demonstrated clinical benefit. The demand for these resources can impact scheduling and availability, potentially affecting other healthcare services and increasing the workload for healthcare providers [96, 97]. This also impacts research as healthcare resources are required for ongoing research to assess the long-term outcomes, risks, and benefits of TRT. The impact of TRT on Primary care providers is also significant. They play a central role in the prescription and management of TRT. The impact on their workload, training needs, and ability to coordinate care for individuals undergoing TRT should be considered in discussions about healthcare resource distribution [98]. Balancing the potential benefits of TRT with the impact on healthcare resources requires thoughtful consideration, evidence-based decision-making and ongoing evaluation. Healthcare systems need to prioritize interventions that provide clear clinical benefits while managing the potential challenges associated with resource utilization and distribution.

#### **MEDIA INFLUENCE AND PATIENT DECISION-MAKING**

##### **Media Portrayal of Hormone Replacement Therapy**

The media's portrayal of Hormone Replacement Therapy (HRT) in middle-aged and elderly men can significantly influence the perception, attitudes, and decisions regarding hormone replacement therapy. Media today when compared to a few years back, depict the perfect male body to be more lean and muscular in various media like movies, magazines, and social media posts; Professional bodybuilders, fitness influencers, and actors use their images and posts on social media to gain added popularity, sponsorship, and market merchandise including supplements; For example, few bodybuilders and other notable members of the movie industry have been open about their steroid use but these are rare [99].

#### **INFLUENCE OF ADVERTISING AND MARKETING ON PATIENT CHOICE**

There has also been a surge in advertising the use of testosterone for conditions not approved by the FDA or in the current guidelines for medical management. Words like "low T" and andropause have gained so much popularity on social media and online forums like Reddit; A reason for this

can be due to the hesitancy of physicians to discuss, explain, and debunk myths for patients who bring up low testosterone discussion, leaving these patients to take the conversation to online forums to gain more knowledge which can most times foster misinformation and self-medication. There is an increase in demand for reducing the effects of aging which draws attention toward the pharmaceutical approach. This is achieved through direct-to-consumer pharmaceutical advertisements and these advertisements give a diagnostic approach that persuades the end user to assume they are affected in this case testosterone deficiency, which may be because of a few non-hormonal factors like poor sleep and nutrition or due to the effects of advanced age. Another way it is achieved is through pharmaceutical company sponsorship of educational materials and magazines for patients with the sole purpose of creating awareness of a condition and the modes of treatments available, leaving the decision-making and choice of treatment to the patient.

#### **ROLE OF PATIENT AUTONOMY AND INFORMED DECISION MAKING**

Patient autonomy and informed decision-making are foundational principles in the ethical practice of medicine. Studies show that the motivation for TRT use among people was to either improve training fitness (70.2%) and body physique (60.26%), with other responses to build self-esteem or image (10.6%). Patients received advice before usage of TRT from physical trainer (70.2%), then also from friends (56.95%), from social media (53.64%), and then self-seeking (38.41%). Another study shows people decide to use TRT due to narcissism, power/control, body image, looks and aesthetics, health, sexuality, media influences, self-esteem, and confidence, while another shows TRT use was to increase muscle mass, increase confidence, to look good, to increase strength, improve mood, decrease fat, attract sexual partners, increase endurance, and improve performance in recreational weightlifting and sports. 52.7% of TRT formulations were obtained from the internet, 16.7% from indigenous sources, 15% from friends or training colleagues, 6.6% from physician's prescription, 5.8% obtained from international countries with less stringent policies on acquiring these medications.

#### **CHALLENGES AND CRITIQUES IN THE MEDICAL COMMUNITY**

In 2020, a coordinated series of trials aptly referred to as the Testosterone trials were done to expand on the risks and benefits of testosterone therapy in hypogonadal men. Despite the numerous benefits of Testosterone replacement therapy, medical professionals often exhibit a certain degree of reluctance in administering this form of treatment. This hesitation can be attributed, at least in part, to the presence of unanswered questions surrounding the effects of testosterone on cardiovascular and cancer risk as the risks could potentially outweigh the benefits. A great example of the different views related to testosterone replacement in the medical community is that of the US Endocrine Society (ES) and the Endocrine Society Of Australia (ESA). Both of these societies recommend testosterone replacement for men with signs and symptoms of androgen deficiency which the ES refers to as organic/classical hypogonadism and the ESA prefers the term pathological hypogonadism. The ES guideline takes into account the controversies regarding testosterone therapy in older men due to a lack of evidence on long-term risks but still considers advanced age (>65 years) in men as a cause of organic hypogonadism. This consideration isn't a license for prescription of testosterone to all men in this age group with sub-normal testosterone concentrations but suggests to experienced clinicians an opportunity to individualize care by having an expansive discussion with select patients that present with severe symptoms, outlining the potential benefits and risks before proceeding with testosterone treatment in those who have made an informed decision. The ESA however excludes older men with low testosterone concentrations, and does not indicate therapy for any patient in the absence of pathological hypogonadism e.g. primary testicular failure (testicular trauma/infection, testes atrophy), secondary testicular failure (hypogonadotropic hypogonadism) via prolactinoma, pituitary tumors, hemochromatosis. These controversies in different organizations make it difficult to centralize treatment with testosterone as there isn't a concrete set of guidelines available globally as seen in other conditions like heart failure, Diabetes mellitus) to treat men who present



with this condition. Thus, management of this condition will have to fall under the discretion of the physician in countries not under the supervision of these bodies which would end up reducing the credibility of treatment and making it unsafe for patients.

#### **FUTURE RESEARCH AND CLINICAL IMPLICATIONS**

Hormone Replacement Therapy (HRT) in middle-aged men has garnered significant attention in recent years. This chapter explores the current understanding of HRT, highlights the importance of future research, and discusses the clinical implications of this therapy. By delving into the potential benefits, risks, and considerations, we aim to shed light on the future of HRT and its impact on middle-aged men's health.

#### **PROPOSALS FOR FUTURE RESEARCH DIRECTIONS IN HRT FOR MIDDLE-AGED MEN**

Wide-ranging research has been done in the field of endocrinology on the probable advantages and disadvantages of HRT in men, scientists are also seeking to identify the best route of administration of exogenous testosterone. More recent research has also suggested that testosterone may have a valuable role in the management of common chronic illnesses and that testosterone may not be a culprit in the pathogenesis of prostate cancer. Here, we suggest a few areas worthy of further research concerning HRT in men.

#### **Benefits of HRT in important chronic illnesses – exploring T2DM and Cardiovascular diseases**

Multiple studies have shown hypogonadism to be related to the development and worsening of diabetes mellitus as well as obesity and dyslipidemia. A study studied the effects of treatment with intramuscular testosterone for 3 months in 24 hypogonadal T2DM men in a placebo-controlled double-blind, crossover trial that showed a decrease in the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) by 1.73 after testosterone therapy compared with placebo. Also, The TIMES2 study which drafted 220 men (average age of 40 years) diagnosed with either T2DM (25%), metabolic syndrome (45%), or both (40%), who also had hypogonadism and/or at least two symptoms of hypogonadism; Patients were randomized to receive testosterone-replacement therapy

to reach normal serum testosterone levels; These patients displayed notable falls in HOMA-IR and HbA1c compared to those on placebo. There was also a substantial decrease in waist circumference, body fat, lipoprotein A, total cholesterol, and LDL-C. Similarly, testosterone therapy has also been studied to identify its potential benefit in the management of certain cardiovascular diseases. The Massachusetts Male Aging Study (MMAS) evaluated 3518 men for over 17 years and men with low testosterone had a 2-fold risk for all-cause mortality and CVD death. 2 large meta-analyses showed that higher testosterone is associated with a lower risk of adverse cardiovascular events in both younger and middle-aged patients. While improvements in cardiac mortality have been seen in multiple studies, some conflicting studies have come to the limelight in recent years, for example a meta-analysis suggested that TRT increases adverse cardiovascular events. Thus, a proposed study to provide a definite answer to the question of whether TRT increases the risk of adverse cardiovascular outcomes is required. It is recommended that it should be a large, placebo-controlled, double-blinded, long-term study (at least 1 year). Key cardiovascular events (MI, Stroke, CV Death) should be the primary endpoint and should be well defined. Furthermore, despite growing evidence that testosterone replacement may be beneficial in the prevention and management of T2DM and Cardiovascular diseases, the current guidelines have no room for testosterone therapy in the management of these common diseases. We also recommend more in-depth studies to assess the potential role of testosterone therapy in the treatment of T2DM and cardiovascular diseases and also to determine the adequate duration and route of treatment in the study population.

#### **FUTURE ALTERNATIVES TO EXOGENOUS TESTOSTERONE THERAPY**

There has been a rapid increase in the use of Testosterone Replacement Therapy (TRT). With new preparations continually being made, patients and clinicians have various selections to choose from with different factors to consider such as efficacy, convenience, cost-effectiveness, accessibility, and safety. Other treatments, including Selective Estrogen Receptor Modulators (SERMs), synthetic gonadotropins,

and aromatase inhibitors, are being used to promote intratesticular and serum testosterone levels while preserving fertility. However, these may have unplanned adverse effects, including a reduction in the quality of semen and consequences for libido and bone mineral density due to changes in estrogen levels. Thus, there is a need to advance approaches to restoring testosterone levels in patients that can both preserve the HPG axis and fertility and also reduce negative side effects. The future of TRT in men desiring to preserve fertility is moving towards endogenous testosterone stimulation through the manipulation of Leydig Stem Cells (LSCs). Innovative therapeutic methods of transplanting LSCs in various animal model testes have shown great promise in this endeavor. Kind to show successful Adult Leydig Cells (ALC) differentiation, increased testosterone production, and preservation of the HPG axis with subcutaneous autograft of LSCs in hypogonadal mice. Further, in vivo studies are needed to assess the efficacy, safety, and clinical applicability of LSC transplant in practice.

#### **THE PARADIGM SHIFT IN PROSTATE CANCER**

Probably the most feared potential complication of hormone replacement therapy in men is prostate cancer. The pathogenesis of prostate cancer has been closely associated with testosterone levels. According to existing guiding principles, a prior or current history of prostate cancer is a contraindication to testosterone therapy. Some studies have shown worsening of LUTS and prostate cancer severity in prostate cancer patients on testosterone therapy. Recent research is starting to show that testosterone may not have a role to play in the development or advancement of prostate cancer. A large systemic review evaluated 11 placebo-controlled and non-placebo-controlled randomized studies in patients with no history of prostate cancer; there was no relation to the development of prostate cancer, Gleason grade, or clinical stage. Even in patients with PIN on previous prostate biopsy, no significant increase in either PSA or incidence of prostate cancer is seen with TRT. It is worthy of note to remember that longer follow-up time is required for prostate cancer compared to other cancers. The long-term effect of hormone replacement

therapy on the development of prostate cancer or progression is yet to be thoroughly studied. It was estimated that a study to determine whether TRT increases prostate cancer risk would need 6000 patients to be treated with testosterone or placebo for 6 years [100]. Thus, the need for larger, national-level studies is required for future research.

#### **RECOMMENDATIONS FOR CLINICIANS AND RESEARCHERS**

An increasing body of research is showing that testosterone has a vital role to play in the homeostasis and maintenance of bodily functions as we age. The use of testosterone therapy stretches past the scope of hypogonadism. It has been shown to have a role in the management of Metabolic syndrome, T2DM, Cardiac health, bone health and depression and is useful in the improvement of LUTS in patients with benign prostatic conditions [101]. Clinicians and researchers are encouraged to explore the use of testosterone therapy beyond the scope of hypogonadism. Further comprehensive research is essential to identify the practicality and safety of testosterone therapy in men and perhaps advance the treatment modalities and general treatment outcomes in these conditions. Given the possible benefits of testosterone therapy in men, it would be advisable for researchers to also dive deeper into the possible side effects of long-term testosterone therapy before promoting its use in anticipated areas of benefit. Judicious and appropriate use of testosterone therapy will be imperative to minimize the theoretical risk of adverse effects, especially in high-risk populations. Further research on large, multi-ethnic cohorts of men through prospective trials to better elucidate both risk and hazard ratios of TRT as it relates to CVD, metabolic disease, prostate cancer, LUTS, obstructive sleep apnea, polycythemia and other yet-to-be-determined theoretical risks of TRT.

#### **IMPLICATIONS FOR THE BROADER FIELD OF MEN'S HEALTH**

Testosterone plays an important role in maintaining physical and mental functions in men. Age-related testosterone deterioration is closely associated with sarcopenia and muscle deterioration, while testosterone decline is

linked with the etiology and prevention of diseases such as angina pectoris, arteriosclerosis, obesity, metabolic syndrome, and dementia. Testosterone replacement has been shown to improve the quality of life in middle-aged and elderly males [102]. Maintenance of testicular function leads to testosterone maintenance which aids in the prevention of testosterone-related diseases such as erectile dysfunction and metabolic syndrome. Lifestyle improvements in diet and exercise which prevent or slow age-related testosterone decline may extend healthy life expectancy [103]. Moreover, Testosterone replacement therapy is expected to have anti-aging effects, thus, averting feebleness and improving quality of life in older individuals. From the standpoint of disease prevention and anti-aging, further functional analysis of testosterone and clinical research development is desirable.

#### CONCLUSION

The emergence and demand for testosterone replacement therapy in middle-aged and elderly men have in no small way been influenced by societal expectations, cultural norms as well as media representations. This is of particular importance as the natural phenomenon of aging is portrayed as a disease, prompting men to worry about losing masculinity (due to a natural decline in testosterone level), therefore making them seek pharmaceutical remedies in the form of hormone replacement; consequently, pathologizing natural variations. The health system has contributed to this anomaly as TRT is rendered to individuals without bearing in mind if other factors, such as diseases or changes in lifestyle routines need addressing. There is however more to TRT than an increase in masculinity as recent research has suggested that testosterone may have a valuable role in the management of common chronic illnesses such as diabetes mellitus, obesity, and dyslipidemia. However, care in dispensing such therapy should be done bearing in mind the frequency of administration, reversibility associated with each administration route as well as care in a patient with comorbidities. Furthermore, protocols/guidelines should be developed to avoid abuse while enhancing the effective and efficient use of these products. This will make supply objective and prevent unnecessary monetization of TRT.

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