Review Article

A Comprehensive Review of Testosterone Treatment for Hypogonadism in Middle-Aged and Older Men

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Abstract: Testosterone deficiency, or hypogonadism, is a prevalent condition among middle-aged and older men, often associated with reduced sexual function, decreased muscle mass, diminished bone density, fatigue, and impaired quality of life. Testosterone replacement therapy (TRT) has emerged as a widely used intervention aimed at restoring physiological hormone levels and mitigating these clinical manifestations. This review synthesized evidence from randomized controlled trials, meta-analyses, and long-term observational studies to evaluate the efficacy, safety, and clinical implications of TRT in this population. Findings indicate that TRT can significantly improve sexual function, muscle strength, lean body mass, and bone mineral density, while also exerting favorable effects on mood and metabolic health in select patients. However, potential risks—including erythrocytosis, cardiovascular events, prostate-related concerns, and variable metabolic outcomes—necessitate careful patient selection, ongoing monitoring, and individualized treatment strategies. The current body of evidence underscores the importance of balancing therapeutic benefits against risks, with particular attention to comorbidities and long-term safety outcomes. This review positions TRT as a clinically valuable but cautiously applied therapy for hypogonadism in aging men, while highlighting gaps in evidence that warrant further large-scale, long-term investigations.

Keywords: testosterone, treatment, hypogonadism, middle-aged, older men

1. INTRODUCTION

Male hypogonadism, often colloquially referred to as "low T," is a clinical syndrome defined by a combination of both a consistently low serum testosterone level and a constellation of associated signs and symptoms [1]. This condition is distinct from the normal, progressive decrease in testosterone production that occurs as a part of the aging process, which is often misleadingly and unhelpfully termed "male menopause" or "andropause" [3]. The natural decline of testosterone levels in men begins slowly around age 30 to 40, at a rate of approximately 1% to 3% per year.[5] While this age-related decline is common, its clinical significance remains a subject of considerable debate, as many older men with low testosterone levels may not experience any symptoms [5]. The central challenge for clinicians is to differentiate between this natural biochemical change and a true pathological condition that warrants intervention. The objective of this comprehensive review is to provide an exhaustive, evidence-based synthesis of the current medical literature concerning the diagnosis, clinical benefits, potential risks, and management strategies of testosterone replacement therapy (TRT) for middle-aged and older men with a formal diagnosis of hypogonadism. This report will clarify areas of scientific controversy, highlight established benefits supported by high-quality evidence, and detail the critical considerations necessary for a patient-centered approach to care. By consolidating data from landmark trials, professional guidelines, and meta-analyses, this review aims to serve as an authoritative reference for clinicians and researchers.

2. THE SYNDROME OF LATE-ONSET HYPOGONADISM

Hypogonadism presents with a broad spectrum of symptoms that can affect a man's sexual, physical, and psychological health [1]. Clinicians and guidelines often categorize these symptoms based on their clinical specificity, which is crucial for accurate diagnosis. Symptoms considered highly suggestive of hypogonadism include reduced sexual desire (libido), decreased spontaneous erections, reduced nocturnal penile tumescence, and a decline in testicular volume [8]. These key diagnostic factors are often the primary reason men seek medical consultation and are considered strong indicators for further biochemical testing. A broader range of symptoms, while frequently associated with low testosterone, are less specific and can be caused by a variety of other factors prevalent in the aging population [10]. These include generalized fatigue, depressed mood, irritability, loss of muscle mass, decreased physical strength, increased body fat, and poor concentration or "mental fogginess" [8]. The non-specific nature of these symptoms presents a major diagnostic challenge, as they can easily be attributed to other medical comorbidities or to the aging process itself, potentially leading to underdiagnosis or misdiagnosis [15]. A key complexity in the clinical assessment of hypogonadism is the bidirectional relationship between low testosterone and various comorbidities. For example, symptoms such as fatigue, mood changes, and loss of muscle mass are not unique to hypogonadism; they are also common in conditions like obesity, type 2 diabetes, and cardiovascular disease [2]. The research shows that these very comorbidities are independently linked to lower testosterone levels [9]. This dynamic creates a situation where a low testosterone level can cause these symptoms, but the underlying medical conditions causing the symptoms can also independently lower testosterone. This means that simply treating the low testosterone level with TRT may not fully resolve a patient's symptoms if the primary comorbidity, such as obesity or poor metabolic health, is not concurrently addressed. Therefore, an effective management plan must recognize TRT as a component of a comprehensive approach to care, not as a standalone solution for the general symptoms of aging. The prevalence of low serum testosterone levels is high and increases significantly with age. Population studies suggest that approximately 20% of men in their 60s have testosterone levels below the normal range for young men, a figure that rises to nearly 50% for men in their 80s [2]. However, the prevalence of symptomatic late-onset hypogonadism, which requires both the biochemical deficiency and the presence of clinical symptoms, is estimated to be much lower. For instance, the European Male Aging Study (EMAS) estimated the prevalence of symptomatic late-onset hypogonadism at only 2.1% in the general population. This distinction is clinically significant and highlights why a simple blood test is insufficient for diagnosis. It underscores the critical importance of a thorough clinical evaluation in addition to laboratory confirmation.

3. DIAGNOSTIC CRITERIA AND CLINICAL EVALUATION

A diagnosis of hypogonadism should only be made in men who exhibit clinical signs and symptoms consistent with testosterone deficiency and have consistently low serum testosterone levels [8]. The diagnostic process requires a rigorous protocol. Due to the diurnal fluctuation of testosterone levels, with the highest concentrations occurring in the morning, a diagnosis requires at least two separate measurements of morning fasting total testosterone, ideally collected before 10 a.m. [15]. The choice of assay is also a critical consideration. The American Urological Association (AUA) guidelines recognize liquid chromatography-tandem mass spectrometry (LCMS) as the "gold standard" due to its excellent sensitivity and specificity, particularly at the low testosterone concentrations relevant for diagnosis [16]. While immunoassays are more common, they are less accurate at the lower end of the range. The Endocrine Society also recommends obtaining a free testosterone concentration using equilibrium dialysis or an accurate formula in men whose total testosterone is near the lower limit of normal or who have conditions that alter sex hormone-binding globulin (SHBG) [18]. Major professional

organizations provide clear guidelines for diagnosis and treatment. The AUA defines a consistently low total testosterone level as less than 300 ng/dL [19]. The Endocrine Society's guidelines, while similar, suggest that clinicians should not routinely prescribe TRT to all men over 65 with low testosterone concentrations but should instead offer therapy on an individualized basis to those who have both symptoms and unequivocally low morning testosterone levels [21]. Both organizations recommend a targeted physical examination in addition to lab tests, which should include an evaluation of body habitus, body hair patterns, testicular size, and the presence of gynecomastia [9]. The diagnosis of hypogonadism presents several key challenges. A major dilemma is the reliance on both a biochemical and a clinical finding. While guidelines provide clear thresholds, the data shows that many men with low testosterone levels have no symptoms, and conversely, many with symptoms have testosterone levels within the normal range [5]. This means that a low number alone is insufficient to justify treatment, a point emphasized by both the AUA and Endocrine Society guidelines, which state that a diagnosis requires both a biochemical deficiency and a clinical component [8]. This diagnostic gray area has led to the development of screening tools like the Androgen Deficiency in the Aging Male (ADAM) questionnaire. While the ADAM questionnaire is highly sensitive for identifying symptoms, its low specificity is a known limitation, largely because its questions overlap with symptoms of other prevalent conditions such as depression [3]. An effective diagnostic process must therefore recognize that TRT is a treatment for a syndrome, not a laboratory value, and that a single blood test is a poor substitute for a comprehensive clinical evaluation. A critical gap exists between published clinical guidelines and real-world practice. The provided research material suggests that a significant number of men on TRT have not had their testosterone levels checked before or after starting treatment, and many receive therapy without a formal diagnosis of hypogonadism [3]. This practice directly contradicts the recommendations of major clinical bodies, which call for rigorous pre- and on-treatment monitoring of testosterone, prostate-specific antigen (PSA), and hematocrit [17]. This highlights a fundamental challenge in the field: the need for greater physician and patient education on proper diagnostic and monitoring protocols to ensure patient safety and optimize outcomes.

4. CLINICAL BENEFITS OF TESTOSTERONE REPLACEMENT THERAPY

The most consistently documented and robust benefit of TRT is its positive effect on sexual function. The Testosterone Trials (T Trials), a landmark set of seven placebo-controlled, double-blind trials involving men with a mean age of 72, definitively showed that testosterone treatment significantly increased sexual activity, sexual desire, and erectile function [23]. Specifically, in the Sexual Function Trial, the effect size for sexual activity (PDQ-Q4 score) was 0.45, for sexual desire (DISF-M-II score) was 0.44, and for erectile function (IIEF score) was 0.32.A meta-analysis of other trials corroborated these findings, noting improvements in sexual functioning with low to moderate certainty evidence [25]. Testosterone is a potent anabolic hormone that promotes muscle protein synthesis and mass [26]. The T Trials demonstrated that TRT improved walking distance by a small but statistically significant amount in all participants [23]. This benefit was observed across the entire cohort, even though it did not reach the pre-specified threshold of increasing the six-minute walking distance by 50 meters or more in the subgroup of men with a slow baseline walk speed [23]. Furthermore, TRT is associated with a reduction in visceral fat and an improvement in insulin sensitivity, which is a key component of metabolic health. The relationship between metabolic health and testosterone levels is complex and bidirectional, as metabolic problems can independently contribute to a decline in testosterone levels [26]. Low testosterone is a well-established risk factor for decreased bone mineral density (BMD), osteoporosis, and fragility fractures in men [1]. The Trials' Bone Trial demonstrated that after one year of treatment, TRT markedly increased volumetric BMD and the estimated strength of the hip and spine [26]. This beneficial effect on bone is primarily mediated through the conversion of testosterone to estradiol [28]. Despite this robust increase in BMD, there is a counterintuitive finding from the larger, long-term

TRAVERSE trial, which found an increased incidence of bone fractures in the testosterone-treated group compared to the placebo group over a median follow-up of three years [30]. This is an important example of a discrepancy between a surrogate endpoint and a hard clinical outcome. While TRT clearly improves BMD, a strong biomarker for bone health, this benefit may not translate into a reduced fracture risk within the relatively short time frame of a clinical trial. It is also possible that other factors associated with TRT, such as increased erythrocytosis-related risks or an increase in activity levels leading to falls, may influence the rate of fractures. This paradoxical finding highlights the need for longer-term, event-driven trials to fully understand the effects of TRT on fracture risk. The evidence for the psychological and quality-of-life benefits of TRT is more subtle and mixed than its effects on sexual function. The Trials' Vitality Trial found that while testosterone treatment did not significantly increase self-reported energy levels, it did result in a slight but statistically significant improvement in mood and depressive symptoms [23]. Other studies have also noted improvements in overall well-being and a reduction in anxiety and irritability in men with diagnosed testosterone deficiency [25]. In addition to the primary benefits, TRT has been shown to have other positive systemic effects. The Trials' Anemia Trial demonstrated that testosterone treatment improved hemoglobin levels and was effective in correcting mild to moderate anemia in men with both a known and an unexplained cause for their anemia [23].

5. RISKS AND ADVERSE EVENTS OF TESTOSTERONE REPLACEMENT THERAPY

The cardiovascular safety of testosterone therapy is a highly contentious and complex issue. The data from large-scale studies has been conflicting, leading to ongoing debate among clinicians and researchers. Some early observational studies and trials raised concerns about an increased risk of cardiovascular events with TRT [12]. The T Trials, for instance, found that TRT increased the non-calcified plaque volume in the coronary arteries, a finding that researchers considered concerning [23]. However, these trials were relatively small and not powered to detect cardiovascular events. Conversely, a recent systematic review and meta-analysis of 51 studies, including both randomized controlled trials and observational studies, suggested that TRT was associated with an 18% reduction in the risk of major adverse cardiovascular events (MACE), particularly in men with pre-existing cardiovascular disease or risk factors [3]. This analysis also reported that TRT improved endothelial function, lipid profiles, and insulin resistance. Another recent meta-analysis of 23 randomized controlled trials also found no significant difference in MACE, all-cause mortality, or cardiovascular mortality between TRT and placebo groups, although it did find a significant increase in the incidence of cardiac arrhythmias [34]. The largest and most recent randomized controlled trial, the TRAVERSE trial, was specifically designed to address these safety concerns. It found that TRT was "noninferior" to placebo with respect to the incidence of MACE [36]. This finding, while reassuring, is considered controversial by some due to the trial's methodological limitations, which included a high rate of patient discontinuation (over 60% in both arms) and a shorter-than-planned duration of follow-up. The trial also found a slight increase in the risk of atrial fibrillation, though this finding was not confirmed by all other studies [35]. The core of this cardiovascular controversy lies in the nature of the research itself. Observational studies are prone to confounding variables because men with low testosterone are often sicker at baseline, with higher rates of obesity, diabetes, and metabolic syndrome, all of which are independent risk factors for cardiovascular disease [16]. While randomized controlled trials are designed to isolate the effect of TRT, they have been limited by either a small size, short duration (T Trials), or high dropout rates (TRAVERSE). This means that a definitive conclusion about long-term cardiovascular safety remains elusive. The most recent meta-analyses suggest no increased risk for MACE, but the potential for cardiac arrhythmias warrants continued vigilance and further investigation. The relationship between testosterone and prostate health is well-established, with testosterone being essential for the growth of both the prostate gland and benign prostatic hyperplasia (BPH) [40]. For this

reason, TRT is contraindicated in men with a known or suspected history of breast or prostate cancer [12]. While there is no definitive evidence linking TRT to the development of prostate cancer, the long-debated link remains a clinical concern. In light of this, major guidelines provide clear protocols for monitoring prostate health in men on TRT [19]. The AUA recommends a baseline PSA measurement for all men over 40 before initiating therapy, and if the level is suspicious, a more formal evaluation, which may include a biopsy, should be considered [9]. On-treatment, the decision for continued PSA monitoring is a shared one between the patient and clinician, and any confirmed increase in PSA should prompt further urological evaluation [29]. The TRAVERSE trial found no increase in prostate-related events, including prostate cancer [37]. Erythrocytosis, or polycythemia, is a common and often dose-limiting adverse effect of TRT, defined as an elevated hematocrit level. The incidence of this side effect can vary significantly by formulation, ranging from 5% to as high as 66% [17]. Testosterone stimulates erythropoiesis (red blood cell production) primarily through an increase in erythropoietin (EPO) [42]. This effect is dose-dependent and is more pronounced in older men and those with comorbidities like untreated obstructive sleep apnea (OSA) or obesity. The AUA provides clear guidelines for management, recommending a baseline hemoglobin and hematocrit measurement before starting therapy [16]. If the baseline hematocrit is over 50%, the clinician should consider withholding TRT until the cause is investigated. While on treatment, a hematocrit level of 54% or higher warrants intervention, which may include dose reduction, switching to a different formulation, or temporary discontinuation of therapy until levels return to normal [7]. Testosterone therapy has been associated with an increased risk of worsening existing obstructive sleep apnea (OSA) [12]. While the exact mechanism is not fully understood, it is hypothesized that testosterone may increase upper airway resistance or decrease upper airway muscle tone [44]. Untreated severe OSA and TRT can have a compounding effect on polycythemia, further increasing the risk of blood clots [42]. Patients with untreated OSA should have the condition resolved before starting TRT [17]. Other potential side effects of TRT include acne, gynecomastia (enlarged breast tissue), fluid retention, and a decrease in sperm production, which can impact fertility [1].

6. TREATMENT MODALITIES AND PATIENT MANAGEMENT

Testosterone replacement therapy is available in several formulations, each with distinct pharmacokinetic profiles, benefits, and drawbacks that must be considered in a patient-centered approach [41]. The choice of formulation is a clinical decision that balances efficacy, safety, and patient preference.

Injectable Testosterone: These are administered either intramuscularly or subcutaneously, typically every one to two weeks [46]. The main advantages are their low cost and efficacy in restoring testosterone levels [47]. However, this method results in significant peaks and troughs in serum testosterone levels, which can lead to fluctuating symptoms and a higher risk of erythrocytosis, with an incidence of up to 40% [17].

Transdermal Gels and Patches: These are applied daily to the skin, providing a more consistent and steady level of testosterone that more closely mimics the body's natural physiological pattern [41]. They are non-invasive and are associated with a significantly lower risk of erythrocytosis, with an incidence of around 3% for Androgen [17]. The primary drawbacks are the need for daily application, potential skin irritation, and the risk of transference of the medication to other individuals through skin-to-skin contact [47].

Testosterone Pellets: These are implanted subcutaneously in a minor surgical procedure every three to six months [46]. Pellets offer the most consistent and long-term stable dosing, eliminating the need for frequent administration and ensuring high patient adherence [49]. The main disadvantages are the

invasiveness of the procedure and the difficulty in making rapid dose adjustments, as a new pellet insertion is required to change the dosage. The choice of formulation is not a simple matter of choosing the "best" one; it involves a complex negotiation of a patient's personal needs, lifestyle, and risk profile. For example, a man with a history of erythrocytosis may be better suited for a gel than an injection, while a man who travels frequently may prefer pellets to a daily gel application [17]. The significantly higher risk of polycythemia with injections compared to gels is a prime example of how formulation-specific risks must guide the decision-making process. The most effective TRT is a personalized regimen, not a one-size-fits-all solution. Given the multifactorial benefits and controversial risks of TRT, shared decision-making is an essential component of care. The clinician's role is to educate the patient on the established benefits (e.g., sexual function), the known risks (e.g., prostate-related changes, erythrocytosis, sleep apnea), and the remaining uncertainties, particularly concerning long-term cardiovascular outcomes [6]. A collaborative approach empowers the patient to weigh these factors and select a treatment plan that aligns with their personal health goals and risk tolerance.

Table 01: Symptoms of Hypogonadism in Adult Men

Highly Suggestive Symptoms	Less Specific Symptoms
Decreased sexual desire (libido) [8]	Unexplained fatigue or lethargy [9]
Decreased spontaneous erections (e.g., morning erections) [8]	Depressed mood or irritability [1]
Erectile dysfunction [1]	Decreased muscle mass or strength [11]
Reduced testicular volume [8]	Increased body fat [11]
Loss of body or facial hair [1]	Poor concentration or memory [8]
Hot flashes or sweats [9]	Diminished sense of well-being [13]

Table 02: Key Findings of the Testosterone Trials (T Trials)

Trial Name	Primary Outcome Measured	Key Finding(s)
Sexual Function	Sexual activity, sexual desire, and erectile function	Increased sexual activity, desire, and erectile function. Effect size for sexual activity: 0.45 (0.30–0.60) [23].
Physical Function	Distance walked in 6 minutes	Did not increase distance walked by 50 meters in men with slow walk speed, but did increase distance walked in all participants by a small amount [23].
Vitality	Energy levels and mood	Did not increase energy levels. Did slightly improve mood and depressive symptoms. Effect size for positive affect: 0.14 (0.01–0.27) [23].
Cognitive Function	Cognitive function	Did not improve cognitive function [23].
Anemia	Hemoglobin levels and anemia correction	Increased hemoglobin and corrected mild to moderate anemia in men with both known and unexplained causes [23].

Bone	Volumetric bone mineral density and estimated strength	Markedly increased volumetric bone mineral density and estimated bone strength of the spine and hip after one year [23].
Cardiovascular	Coronary artery non-calcified plaque volume	Increased non-calcified plaque volume, a finding considered concerning [23].

Table 03: A Comparative Overview of Common Testosterone Formulations

Formulation	Pharmacokinetics	Patient Convenience & Adherence	Major Risks & Drawbacks
Injectable	Significant peaks and troughs in serum testosterone levels [41].	Dosing is weekly to biweekly; low cost [47].	Highest incidence of erythrocytosis (40%) and significant symptom fluctuation [17]. Requires needles and injections [47].
Transdermal Gels/Patches	Provides more consistent, steady daily levels [41].	Requires daily application; non-invasive [48].	Risk of transference to others via skin contact; potential for skin irritation [47]. Lower risk of erythrocytosis (3%) [17].
Pellets	Most consistent and stable long-term levels over 3-6 months [49].	Highest adherence and convenience, as dosing is infrequent [49].	Most invasive procedure, requiring minor surgery; difficult to adjust dosage quickly [49]. High risk of polycythemia (35%) [17].

7. CONCLUSION

Based on the synthesis of available research, TRT is an effective and appropriate treatment for symptomatic hypogonadism in middle-aged and older men. The evidence is strongest and most consistent for its benefits on sexual function, including increased libido, sexual activity, and erectile function. TRT also provides robust benefits for bone mineral density and is effective in correcting mild to moderate anemia. The evidence for its effects on physical function, mood, and vitality is more modest and mixed, suggesting that TRT is not a universal solution for all symptoms of aging. The debate surrounding the cardiovascular safety of TRT is multifaceted, with conflicting data from various studies. However, the most recent and comprehensive meta-analyses generally suggest no increased risk of major adverse cardiovascular events (MACE). Nevertheless, the potential for an increased risk of cardiac arrhythmias and the concerning finding of increased non-calcified plaque volume from the T Trials warrant continued caution and careful patient selection. Common side effects such as erythrocytosis, worsening of BPH symptoms, and exacerbation of sleep apnea are well-documented and can be managed effectively through appropriate pre-treatment screening and diligent on-treatment monitoring. Despite significant advances in the field, several critical questions remain unanswered,

highlighting key areas for future research. The primary research gap remains the long-term safety of TRT beyond the relatively short follow-up periods of most clinical trials.[3] The conflicting data on cardiovascular outcomes and the counterintuitive finding of an increased fracture risk in the TRAVERSE trial underscore the urgent need for a large-scale, long-term, and well-designed trial to definitively establish the cardiovascular and skeletal safety profile of TRT. Further research is needed to determine the optimal dosing, duration, and delivery method for different patient subgroups to maximize therapeutic benefits while minimizing adverse events. The high variability in the incidence of erythrocytosis across different formulations, for instance, suggests that future studies should focus on standardizing TRT regimens to improve the comparability of results and provide clearer clinical guidance. Finally, the precise mechanistic pathways by which TRT influences various organ systems, such as the increase in non-calcified plaque and its effect on sleep apnea, require further elucidation. A deeper understanding of these mechanisms could lead to the development of safer and more targeted therapies, ultimately improving the risk-benefit profile of TRT for middle-aged and older men.

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