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REVIEW

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Novel perspectives of testosterone therapy in men with functional hypogonadism: traversing the gaps of knowledge

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ABSTRACT

Introduction: In the past decade, there has been a significant augmentation in the corpus of evidence pertaining to functional hypogonadism. Despite this, prevailing clinical guidelines continue to advise against the universal screening for hypogonadism in middle-aged and elderly males.

Findings: Numerous randomized controlled trials have scrutinized the effects of testosterone therapy in males afflicted with type 2 diabetes and/or obesity. However, these guidelines uniformly assert that lifestyle modifications and weight reduction should be the primary intervention strategies in overweight and obese males, relegating testosterone therapy to a secondary, selective option. It is extensively documented that testosterone therapy can yield substantial improvements in various metabolic parameters as well as ameliorate symptoms of erectile dysfunction. Moreover, recent studies have demonstrated the potential of testosterone therapy in reversing type 2 diabetes in males with low-normal testosterone levels who are at elevated risk for this condition, in comparison to the outcomes achievable through lifestyle modifications alone.

Conclusion: This focused review article aims to present a comprehensive update on the latest data concerning the innovative aspects of testosterone therapy in males with functional hypogonadism, particularly in the context of type 2 diabetes and/or obesity. Additionally, it will delve into the cardiovascular safety of such interventions within this high-risk demographic, with a special emphasis on insights gleaned from the TRAVERSE trial.

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1. Introduction

Functional hypogonadism in men is characterized by the concurrent manifestation of clinical features indicative of androgen deficiency and decreased serum testosterone levels, occurring in the absence of organic pathology within the hypothalamic-pituitary-testicular (HPT) axis and without specific pathological conditions that suppress the HPT axis in middle-aged or older men [1]. Distinct from classical (organic) hypogonadism, functional hypogonadism is potentially reversible, contingent upon the identification and effective treatment or removal of its underlying causes [2]. The vast majority of functional hypogonadism cases are associated with aging and comorbidities such as obesity, type 2 diabetes mellitus (T2D), or metabolic syndrome (MetS) [3]. The estimated prevalence of low testosterone in men with these comorbidities is approximately 50% [4]. Conversely, low total testosterone levels are linked with an elevated risk of T2D development, with odds ratios ranging from 1.6 for levels below 16 nmol/L to 4.5 for levels below 8 nmol/L [5]. Furthermore, a total testosterone level below 8.7 nmol/L is associated with an increased waist circumference and a heightened risk of cardiovascular mortality [6].

Over the past two decades, there has been a notable surge in awareness of male functional hypogonadism, a condition that has historically been under-diagnosed and under-treated [7]. Numerous randomized controlled trials (RCTs) have been conducted to assess the impact of testosterone therapy (TTh) in men with T2D and/or obesity. While it is established that TTh contributes to the amelioration of

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various MetS parameters and erectile dysfunction, its effects on cognitive function, mobility, and bone health have shown inconsistent results [8].

Current guidelines advocate for lifestyle changes and weight reduction as the primary intervention strategies for overweight and obese men [1,9]. The utility of TTh in middle-aged to older men with functional hypogonadism remains a topic of debate and contention. These guidelines do, however, support the initiation of TTh for a minimum period of six months in these men, to evaluate the emergence of clinical benefits [2]. A recent multi-centric study involving obese men with low-normal testosterone levels and a high risk of T2D demonstrated that a combination of lifestyle modifications and TTh over a two-year period not only improved metabolic parameters but also reversed newly diagnosed T2D [10]. This evidence points towards a novel pharmacological approach for T2D prevention in men experiencing obesity-associated functional hypogonadism [11].

This focused review article aims to deliver an encompassing overview of the innovative dimensions of TTh in men with functional hypogonadism, particularly those cases associated with T2D and/or obesity. Additionally, we will emphasize the cardiovascular safety concerns related to testosterone deficiency and its replacement therapy in this high-risk demographic population. This will include an exploration of the latest research findings and clinical insights, providing a comprehensive understanding of the potential risks and benefits of TTh in managing functional hypogonadism amid the complexities of T2D and obesity.

2. Functional hypogonadism: clinical implications, characteristics and diagnosis

Functional hypogonadism is delineated as a clinical and biochemical syndrome, characterized by the simultaneous presence of clinical features of androgen deficiency and reduced serum testosterone levels. This condition occurs in the absence of intrinsic structural pathologies of the HPT axis, such as Klinefelter syndrome or pituitary tumors, as well as specific pathological conditions that suppress the HPT axis, like Cushing's syndrome or prolactinoma, particularly in middle-aged or older men [2].

Unlike organic (classical) hypogonadism, which is generally irreversible, functional hypogonadism may be potentially reversible if its underlying causes are identified and appropriately addressed or eliminated [2,12]. However, in a minority of cases, secondary hypogonadism can be linked to other potentially reversible conditions, such as the use or abuse of opiates or anabolic androgens, as well as hyperprolactinemia [13]. Functional hypogonadism pertains to functional disruption of the HPT axis rather than genetic causes or pathological disturbances of the axis itself [12]. The vast majority of functional hypogonadism cases are associated with aging and comorbidities such as obesity, T2D, or MetS. In the context of obesity, several mechanisms can lead to secondary hypogonadism, including central factors (like decreased endogenous kisspeptin, chronic inflammation with insulin and leptin resistance), peripheral factors (such as high leptin levels, decreased SHBG, gut endotoxin), and testicular factors (including increased intrascrotal temperature and inflammation of the epididymis), all of which may impact the HPT axis [14].

Functional hypogonadism is typified by a less pronounced reduction in testosterone levels compared to organic hypogonadism [15]. The association between functional hypogonadism and metabolic disorders is complex, multifaceted, and bidirectional, involving disruption of the HPT axis [16]. Practically any acute or chronic illness can either mimic or obscure the clinical manifestations of testosterone deficiency and lead to functional suppression of the HPT axis [1].

Estimates of the prevalence of functional hypogonadism in middle-aged and older men vary considerably, ranging from 2.1% to 12.3% [12]. Lower testosterone concentrations have been inversely correlated with cardiovascular (CV) risk factors, including BMI, waist circumference, elevated blood sugar, and arterial hypertension [17,18]. Consequently, men with lower testosterone levels are more prone to insulin resistance (IR), visceral obesity, and are at an increased risk of developing MetS or T2D [19,20]. About 50% of males aged over 40 years with T2D and/or MetS present with decreased total testosterone levels [21].

The signs and symptoms of hypogonadism are diverse and depend on the age at onset, etiology, and severity of the decrease in testosterone levels [22]. In adults, pathognomonic symptoms are typically sexual in nature, encompassing erectile dysfunction, diminished libido, and reduced frequency of morning erections. Additionally, a range of nonspecific physical and psychological symptoms may be present, such as fatigue, impaired concentration or memory, reduced vitality, walking difficulties, sweating, depressive mood, decreased strength or endurance, reduced capacity for sports, and a tendency to fall asleep after dinner [1,22].

Physical examinations of individuals with hypogonadism often reveal increased body fat, decreased

muscle mass and body hair, gynecomastia, reduced testicular volume, thin and dry skin, and signs of anemia. A notable decrease in muscular strength can elevate the risk of falls, which, coupled with decreased bone mineral density (BMD), heightens the risk of bone fractures in men with lower testosterone levels [23]. The symptoms of hypogonadism can be semi-quantitatively assessed using the Aging Male Symptoms (AMS) questionnaire, primarily utilized as an initial step in evaluating the effects of testosterone replacement therapy [24]. However, due to the low specificity of the AMS questionnaire, it is not suitable for the diagnosis of hypogonadism. Clinical examination of men suspected of hypogonadism should include anthropometric measurements like BMI and waist circumference, assessment of body hair, breast and genital examination, as well as spine examination [25].

The diagnosis of functional hypogonadism necessitates the exclusion of organic causes of hypogonadism. The diagnostic criteria for functional hypogonadism include the concurrent presence of low serum testosterone levels (total testosterone $<$11 nmol/L and free testosterone $<$220 pmol/L) and three specific sexual symptoms: erectile dysfunction, decreased libido, and reduced frequency of morning erections [9,26]. The most precise and accurate method for determining serum testosterone concentrations is liquid chromatography-tandem mass spectrometry (LC-MS/MS).

To enhance diagnostic accuracy, it is advised that testosterone levels be measured in the fasting state, preferably between 7 and 11 am, and on at least two different days to account for biological variability in circulating testosterone levels. In cases where patients exhibit marginally decreased testosterone concentrations (ranging from 8 to 12 nmol/L), or in patients with conditions affecting sex hormone-binding globulin (SHBG), it is recommended to measure or calculate free testosterone in addition to total testosterone [9]. This approach ensures a more comprehensive assessment of testosterone status, particularly in borderline or complex cases.

3. Benefits of testosterone therapy on parameters of metabolic syndrome

Men with low testosterone levels who also have obesity and/or T2D demonstrate increased insulin resistance, often attributed to factors like high BMI, elevated fat mass, and a higher waist-to-hip ratio, compared to eugonadal men with T2D [27]. Several RCTs have investigated the effects of TTh on insulin resistance and other MetS parameters in men with functional hypogonadism and T2D, yielding inconsistent results. Some studies have reported a statistically significant reduction in insulin resistance [27–32], while others, particularly smaller studies with shorter durations, observed no change [33–35].

One study examining the impact of TTh over three months in 24 hypogonadal men with T2D found that the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) index decreased by 1.73 compared to a placebo group [30]. Additionally, research comparing the efficacy of TTh and lifestyle changes has been conducted. In an RCT by Heufelder et al. 32 men with MetS and newly diagnosed T2D, with total testosterone levels below 12 nmol/L, were prescribed a diet and exercise regimen. Half of these participants were also administered transdermal testosterone for 52 weeks. The group receiving TTh exhibited greater statistically significant improvements in insulin sensitivity (measured by HOMA-IR; −0.9) compared to the group following diet and exercise alone [36]. In a multi-centric RCT, one year of transdermal TTh in 220 hypogonadal men with T2D and MetS resulted in a statistically significant 15% decrease in HOMA-IR [32]

In a randomized controlled trial (RCT) involving 55 obese men with functional hypogonadism and T2D, one year of TTh led to notable reductions in the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), fasting plasma glucose levels, HbA1c, and total cholesterol levels. Additionally, there was an improvement in the flow-mediated dilation (FMD) of brachial arteries and the intima-media thickness (IMT) of carotid arteries [28]. Extending TTh to two years further enhanced glycemic control, insulin resistance, dyslipidemia, and endothelial function, while also restoring serum testosterone levels well within the normal range [29].

Other studies have indicated that TTh results in a significant reduction in fat mass and improvement in body composition, which are beneficial metabolic effects [37,38]. The influence of TTh on insulin sensitivity can be attributed to various mechanisms, including the loss of subcutaneous fat, gain in muscle mass, and a decrease in circulating free acids [39]. At the cellular level, testosterone increases the expression of several key components involved in glucose metabolism. These include the insulin receptor β subunit, insulin receptor substrate 1 (IRS-1), RAC-beta serine/threonine-protein kinase AKT2, and glucose transporter type 4 (GLUT-4) in adipose tissue. Additionally, it enhances adenosine 5′-monophosphate-activated protein kinase α (AMPK α) expression and activity in skeletal muscle. AMPK α promotes the phosphorylation and activation

of AKT kinase, leading to the translocation of GLUT-4 to the membrane, thereby increasing glucose transport [40]. This mechanism, functioning independently of insulin action, can enhance insulin signal transduction, as insulin action also involves AKT kinase and GLUT-4. The role of AMPK α is crucial in mediating the effects of exercise and augmenting glucose transport [39]. Results from a study involving 32 men treated with intramuscular testosterone for 22 weeks showed that TTh leads to an increase in AMPK α expression and phosphorylation [41], suggesting a potential mechanism by which TTh could improve insulin signal transduction [39].

Another pivotal mechanism by which testosterone ameliorates insulin resistance is through its anti-inflammatory properties [27]. Research has indicated that pro-inflammatory cytokines, such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1beta (IL-1β), can inhibit testosterone secretion by affecting the HPT axis [42]. The hypothesis that testosterone possesses anti-inflammatory effects *in vivo* stems from two primary observations: (a) testosterone deficiency is linked with elevated levels of inflammatory cytokines; (b) testosterone supplementation has been shown to reduce the levels of these inflammatory cytokines. Testosterone is believed to exert its anti-inflammatory effects, in part, by modulating the secretion of cytokines from adipose tissues and immune cells.

However, the extent and clinical significance of testosterone's anti-inflammatory effects are subjects of ongoing debate. While some studies support the notion that testosterone can significantly reduce inflammatory markers, others have reported that the impact of testosterone on inflammation is clinically negligible [43]. This discrepancy suggests the need for further research to fully understand the relationship between testosterone and inflammatory processes, particularly in the context of insulin resistance and metabolic disorders.

The findings from a long-term study (spanning 8 years) on TTh in men with prediabetes and low testosterone are particularly noteworthy. Yassin et al. conducted a study comparing 229 men with prediabetes and hypogonadism who were treated with testosterone undecanoate (T-group) to 87 men who chose not to undergo TTh (untreated controls) [44]. At the study's onset, 161 (51%) of the patients were obese, 136 (43%) were overweight, and 19 (6%) had normal weight. The results were quite noteworthy: the T-group achieved an average weight loss of 8.8 ± 0.4%, whereas the untreated group experienced an average weight gain of 9.1 ± 1.3%. Specifically, body weight decreased by 9.2 ± 0.4 kg in the T-group and increased by 8 ± 1.3 kg in the untreated group. Similarly, waist circumference decreased by 6.8 ± 0.3 cm in the T-group, in contrast to an increase of 7.4 ± 1 cm in the untreated group.

These findings suggest that weight loss in response to TTh may be a key factor in preventing the progression of prediabetes to diabetes. A weight reduction of 10% is considered to maximally prevent future diabetes in patients with prediabetes or MetS [45]. However, achieving and maintaining such weight loss through diet and exercise alone can be challenging [46]. Another factor contributing to the prevention of the progression of prediabetes to diabetes is the consistent increase in lean body mass observed with TTh [38]. Research has shown that a larger muscle mass is linked with higher insulin sensitivity, lower HbA1c levels, and a reduced risk for prediabetes and overt T2D in both older and younger men with hypogonadism [47]. The primary mechanism by which TTh is thought to prevent the development of diabetes is through improvement in insulin sensitivity [30], highlighting the potential role of TTh as a therapeutic option in managing prediabetes and preventing its progression to T2D.

The results of an even more extended trial, spanning 11 years and involving 823 hypogonadal men (57.6% obese, 34.8% overweight, and 7.7% with normal weight), further underscore the efficacy of TTh in reducing body weight, waist circumference, and BMI [48]. In the group receiving TTh, weight decreased by 3.4 ± 1.2 kg among 26 men with normal weight, by 8.5 ± 0.4 kg among 113 overweight men, and by 23.2 ± 0.3 kg among 281 obese men. Conversely, in the control group (395 men not treated with TTh), an increase in body weight was observed: 6.1 ± 0.7 kg in 37 men with normal weight, 6.0 ± 0.3 kg in 167 overweight men, and 4.2 ± 0.5 kg in 193 obese men.

When analyzing relative weight change, men with normal weight on TTh lost 4.8 ± 1.5%, while untreated men gained 8.0 ± 0.9%. Overweight men on TTh lost 9.6 ± 0.4%, while untreated men gained 6.9 ± 0.3%. Obese men on TTh lost 20.6 ± 0.3%, while untreated obese men gained 5.1 ± 0.4%. These changes in weight, both with and without TTh, across all three groups were reflected in corresponding shifts in BMI.

Specifically, among participants with normal weight, waist circumference decreased by 3.4 ± 0.8 cm in those receiving TTh, compared to an increase of 5.5 ± 0.5 cm in untreated men. In overweight men, waist circumference decreased by 4.7 ± 0.3 cm among those receiving TTh and increased by 5.5 ± 0.2 cm in untreated men. In

the obese group, waist circumference decreased by 12.9 ± 0.2 cm among men on TTh and increased by 5.6 ± 0.4 cm in untreated men.

The relative weight loss in patients receiving TTh—approximately 5% in the normal weight subgroup, 10% in the overweight subgroup, and 20% in the obese subgroup—represents a significant weight loss, previously unmatched by other therapeutic interventions except bariatric surgery. Other notable effects of TTh in this study include statistically significant differences between groups in glycemic control, blood pressure, pulse pressure (the difference between systolic and diastolic pressure), lipid profiles (increased HDL levels, decreased total cholesterol (TC), LDL, and triglycerides (TG) levels, and marked reductions in non-HDL cholesterol), and quality of life improvements. Most importantly, the progressive and sustained weight loss observed in all three subgroups on TTh contributed to a reduction in cardiovascular mortality.

The Testosterone for Diabetes Mellitus (T4DM) trial, which involved 1007 men with abdominal obesity, a total testosterone level of 14 nmol/L or less, and impaired glucose tolerance or newly diagnosed T2D, provides insightful data on the efficacy of TTh. Over two years, participants in this study were administered testosterone undecanoate, and the effects of this treatment were compared to those of lifestyle interventions and placebo. The study was meticulously designed to evaluate the efficacy and safety of TTh, and all participants were prescribed the same diet and exercise program while being randomly assigned to receive either TTh or a placebo [10].

The results of the T4DM trial revealed several significant changes in various parameters in the testosterone group compared to the group that only underwent lifestyle modifications. Notably, improvements in body composition, a decrease in visceral fat, and an increase in total muscle mass were observed in the testosterone group. In contrast, the non-testosterone group experienced a decrease in total muscle mass and an increase in visceral fat. Specific measurements showed that the waist circumference decreased more in the testosterone group (−6.99 cm) compared to the placebo group (−4.85 cm). Similarly, the total fat mass reduction was more substantial in the testosterone group (−4.60 kg) than in the placebo group (−1.89 kg), and the decrease in abdominal fat mass was also more pronounced (−3.55% vs. −1.21%). Moreover, while the total muscle mass increased in the testosterone group (+0.39 kg), it actually decreased in the placebo group (−1.32 kg).

Additionally, the group receiving testosterone therapy showed greater improvements in sexual health parameters, as assessed by the International Index of Erectile Function subscales [10]. These findings underscore the potential benefits of TTh in men with low testosterone levels, especially in the context of managing body composition and sexual health in those with T2D or impaired glucose tolerance.

In various studies, testosterone therapy (TTh) has been observed to lead to improvements in lipid profiles [30,35,42,48] and to reduce the severity of non-alcoholic fatty liver disease (NAFLD) [49,50]. These beneficial outcomes are largely attributed to the decrease in body weight and the improvement in insulin resistance achieved through TTh [29].

Significant evidence from larger RCTs, such as the Testosterone Trials (TTrials), indicates that TTh provides a range of metabolic benefits. Notably, one year of TTh has been shown to improve all aspects of sexual function, enhance walking distance, elevate mood, alleviate depressive symptoms, correct mild to moderate anemia, markedly increase volumetric bone mineral density and estimated bone strength, and increase coronary artery plaque volume [51]. Additionally, TTh has been associated with improvements in vitality, mood, and cognitive function [52], offering further benefits in treating symptoms associated with testosterone deficiency.

Low testosterone levels can adversely affect motivation, potentially hindering the adoption of healthy lifestyle measures. Several studies have suggested that TTh can boost motivation for engaging in healthy eating habits and regular exercise [2]. This aspect of TTh is particularly relevant, as motivation plays a crucial role in the successful implementation and maintenance of lifestyle changes essential for managing conditions like obesity, T2D, and metabolic syndrome. By enhancing motivation and facilitating adherence to healthier lifestyles, TTh can contribute significantly to the overall management and improvement of health outcomes in men with testosterone deficiency.

4. Testosterone therapy for prevention and reversion of type 2 diabetes

Several RCTs have investigated the effects of TTh on insulin resistance and glycemic control in men with functional hypogonadism and T2D, yielding mixed results. Some of these studies have demonstrated a statistically significant reduction in HbA1c levels [28,29,31,32], indicating an improvement in long-term glycemic control.

A study by Heufelder et al. found that combining TTh with lifestyle changes led to greater improvements in glycemic control compared to lifestyle changes alone. A notable strength of this study is that the participants were not on any glucose-lowering medications during the study period, allowing for a clearer assessment of the effects of TTh and lifestyle modifications on glycemic control [36].

Similarly, a study by Yassin et al. observed that eight years of TTh treatment not only prevented the onset of T2D but also normalized glycemia (fasting plasma glucose and HbA1c) and significantly reduced the risk of cardiovascular events and mortality compared to matched controls who did not receive testosterone. Remarkably, none of the men with hypogonadism and prediabetes treated with TTh progressed to overt T2D, whereas 40.2% of the untreated men with similar conditions developed overt T2D. In this study, TTh led to substantial improvements in glycemic parameters, with HbA1c decreasing by $0.39 \pm 0.03\%$ in the T-group, in contrast to an increase of $0.63 \pm 0.1\%$ in the untreated group [44].

Furthermore, a longer treatment period of 11 years with TTh in 428 hypogonadal men demonstrated that TTh effectively prevented the progression from prediabetes to T2D, irrespective of baseline weight [48]. In contrast, the control group (395 men not treated with TTh) exhibited an increase in fasting blood glucose and HbA1c levels. These findings collectively underscore the potential of TTh as a therapeutic strategy to improve glycemic control and prevent the progression of prediabetes to T2D in men with functional hypogonadism.

The study by Haider et al. provides compelling evidence on the long-term benefits of TTh in patients with T2D and hypogonadism. Over an 11-year period, TTh led to the remission of diabetes in one-third of the patients and also improved insulin sensitivity. The study also reported significant changes from baseline in response to TTh in various anthropometric variables and lipid profiles, including non-HDL and remnant cholesterol levels. These improvements suggest a potential reduction in the risk of cardiovascular disease in patients with T2D who are treated with TTh [53].

In the Testosterone for Diabetes Mellitus (T4DM) trial, the main observation was the regression of T2D in participants with newly detected T2D at baseline who were treated with TTh [10,11]. Initially, the prevalence of T2D was 19.9% (88 of 443 participants) in the testosterone group and 20.3% (84 of 413 participants) in the placebo group. After two years, the prevalence of T2D decreased to 12.4% (55 of 443 participants) in the testosterone group, while it remained at 21.4% (87 of 413 participants) in the placebo group, corresponding to a significantly reduced risk for T2D by 41% in the testosterone group. Subgroup analysis revealed that among men with prediabetes at baseline, 7.6% of the testosterone group progressed to T2D, compared to 14% of the placebo group. Among men with newly diagnosed T2D at baseline, 31.8% in the testosterone group still had T2D, compared with 45.2% in the placebo group.

The study observed a statistically significant reduction in fasting plasma glucose and an approximately 40% reduction in the relative risk of developing new onset T2D after two years of TTh over lifestyle interventions. However, the investigators found no effect of TTh on HbA1c concentration, which remains not fully understood. One explanation offered by the authors is that the erythropoietic effects of testosterone may be confounding the HbA1c results [11]. This observation highlights the complexity of TTh's effects on diabetes management and the need for further research to fully understand its impact on various metabolic parameters.

5. Impact of testosterone therapy on bone health

Testosterone deficiency is a significant contributing factor to secondary osteoporosis and low trauma fractures in males [54]. The impact of TTh on bone health in hypogonadal men, however, remains a subject of ongoing debate and research [55]. Results from various randomized studies have been conflicting, with some indicating positive effects of testosterone replacement therapy on BMD, particularly in the lumbar spine region of testosterone-deficient men. It is important to note, though, that none of these studies had their primary objective focused on assessing the impact on fracture incidence reduction [56].

In younger hypogonadal men, TTh has been shown to prevent further bone loss and assist in achieving the genetically determined maximal bone mass [57]. However, the role of TTh in older men with osteopenia or osteoporosis and hypogonadism is less certain. While testosterone does increase lumbar spine BMD compared to controls, there is an elevated risk of treatment complications in older men compared to their younger counterparts [58].

From the Testosterone Trials (TTrials), there is evidence suggesting that TTh improved volumetric bone density and estimated bone strength in the lumbar spine and at the hip, with more pronounced benefits

observed in the lumbar spine and trabecular bone [59]. Additionally, the T4Bone study, which is a part of the T4DM study, examined the effects of TTh on bone microarchitecture over a period of 2 years. This study demonstrated an improvement in cortical and total BMD in a group of men who received testosterone supplementation [60]. These findings contribute to the growing body of evidence supporting the potential benefits of TTh in enhancing bone health, especially in men with testosterone deficiency. However, the precise role of TTh in bone health management, particularly in older men, warrants further investigation to fully understand its benefits and associated risks.

Men with functional hypogonadism undergoing replacement therapy can anticipate that testosterone will aid in preventing further bone loss and in increasing BMD, particularly in those with very low baseline serum testosterone levels [61]. The degree of BMD improvement with testosterone therapy (TTh) is proportional to the severity of hypogonadism [62]. However, it's important to note that TTh in men with functional hypogonadism and osteoporosis increases BMD to a lesser extent than anti-osteoporosis medications do [63]. Currently, there is no evidence to suggest that TTh alone reduces the risk of osteoporotic fractures.

Therefore, for men with functional hypogonadism who have severe osteoporosis or are at a very high risk for bone fractures, it is recommended that TTh be combined with anti-osteoporosis drugs that have proven efficacy in reducing fracture risk [54]. This combined approach is critical in optimizing bone health and minimizing fracture risk in this population.

Additionally, TTh is effective in promoting bone anabolism and preventing sarcopenia (age-related loss of muscle mass and strength). It also improves physical performance, which is a crucial factor in mitigating falls and frailty, both of which are key contributors to the occurrence of fractures, especially femoral bone fractures [64,65]. By enhancing muscle strength and overall physical condition, TTh can play a significant role in reducing the risk of falls and related complications, which is particularly beneficial for older men with functional hypogonadism.

6. Impact of testosterone therapy on cardiovascular system

Testosterone deficiency is linked with several metabolic disorders, including visceral obesity, dyslipidemia, a pro-inflammatory state, insulin resistance, and T2D. Consequently, men with hypogonadism face a significantly heightened risk of mortality, which is more than double that associated with all cardiovascular diseases combined. Diabetes and MetS independently pose very high risks for cardiovascular events and mortality [2].

Testosterone plays a diverse role in cardiovascular physiology, with some of its physiological effects potentially reducing cardiovascular risk. These include coronary vasodilation and increased coronary blood flow, improved vascular reactivity, increased muscle mass, reduction in whole body and visceral fat mass, shortening of the corrected QT (QTc) interval, and normalization of glycemia during lifestyle interventions for prediabetes [1,10]. Additionally, some RCTs have shown that TTh reduces IMT and improves endothelial function, which are surrogate markers of atherosclerosis [28,31,66].

Clinical data suggests that low testosterone levels are associated with longer heart-rate QTc intervals and that TTh can result in the shortening of these intervals. Prolonged heart-rate QTc intervals are known to increase the incidence of ventricular arrhythmias and the risk of sudden cardiac death [67].

Furthermore, preclinical studies indicate that testosterone has vasodilatory effects. This process is thought to involve the downregulation of L-type voltage-gated calcium channels [68] and the upregulation of calcium-activated potassium channels [69]. These findings highlight the complex and multifaceted impact of testosterone on cardiovascular health and suggest that managing testosterone levels could be a key component in reducing cardiovascular risk in men with hypogonadism.

The immediate vasodilatory effects of testosterone have prompted questions about the possibility of non-genomic actions underlying this mechanism. Additionally, testosterone has been shown to increase cardiac contractility [70], further highlighting its significant cardiovascular effects.

In a retrospective study of 83,010 male veterans with documented low total testosterone levels, Sharma et al. explored the relationship between the normalization of total testosterone levels after TTh and cardiovascular (CV) events, as well as all-cause mortality, in patients without a prior history of myocardial infarction (MI) or stroke. This extensive observational cohort study with extended follow-up found that normalization of total testosterone levels after TTh was associated with a significant reduction in all-cause mortality, MI, and stroke. This study was pivotal in demonstrating that significant benefits are observed only if TTh is sufficient to normalize total testosterone levels. Patients who did not achieve the therapeutic range after TTh did not

experience a reduction in MI or stroke and had less benefit in terms of mortality [71].

Some observational studies [72] have reported inverse correlations between testosterone levels and IMT, a surrogate marker for atherosclerosis. However, due to the observational nature of these studies, reverse causality cannot be discounted. While there is a shortage of RCTs directly addressing atherosclerosis, some have reported on carotid IMT and plaque calcification. For instance, a small RCT noted significant beneficial effects of testosterone on carotid IMT [73], whereas larger trials, such as the Testosterone Trials (TTrials), have not corroborated this finding.

Testosterone may also influence plaque stability through its effects on endothelial progenitor cells, which play a role in maintaining vessel integrity and are inversely related to carotid IMT. It has been observed that men with hypogonadism have lower levels of endothelial progenitor cells, but these cells seem to increase in proliferation and migration in a manner dependent on the androgen receptor (AR) [74]. These findings underscore the complex and multifaceted impact of testosterone on cardiovascular health, highlighting the potential for TTh in managing cardiovascular risks, particularly in men with hypogonadism.

Dyslipidemia, marked by elevated levels of low-density lipoprotein (LDL) and total cholesterol, is a significant risk factor for the progression of atherosclerosis. Testosterone has been identified to possess prothrombotic effects, which potentially increase the risk of myocardial infarction (MI) and stroke following the rupture of atherosclerotic plaques. The proposed mechanisms for this include the stimulation of hematocrit, which induces platelet aggregation, and an increase in thromboxane A2 receptor density on platelets [75]. However, it is noteworthy that clinical trials have not observed these effects on coagulation factors [76].

There has been a concern, primarily derived from studies involving subjects with an undiagnosed family history of thrombophilia-fibrinolysis, about a possible increased risk of venous thromboembolism (VTE) in men undergoing TTh [77]. The most comprehensive and updated meta-analysis, which includes data from 13 RCTs encompassing 5050 subjects with hypogonadism on TTh, does not support an association between TTh and an increased risk of VTE [78]. Nonetheless, some guidelines do recommend conducting a thorough family history evaluation to exclude thrombophilia-fibrinolysis before initiating TTh [7].

This discrepancy between theoretical risks and clinical trial findings highlights the complexity of testosterone's effects on cardiovascular health and the need for careful patient evaluation and monitoring when considering TTh, especially in populations at risk for cardiovascular events.

7. Adverse cardiovascular events and mortality

In recent years, several individual observational studies and one randomized trial [79–81] have indicated potentially increased risks for cardiovascular morbidity and mortality among certain groups of men receiving TTh. This presents a contrast to the growing body of evidence that suggests the beneficial effects of testosterone replacement therapy on cardiovascular diseases. It is important to note, however, that these studies had methodological limitations, which make it difficult to draw definitive and firm conclusions.

Finkle et al. reported an increased risk of myocardial infarction (MI) in men with pre-existing heart disease who received TTh. In their analysis of 55,593 men on testosterone replacement therapy, they observed that the risk of heart attack in men with known heart disease was twice as high in the 90 d after starting TTh compared to the year before starting the therapy. They also found that men over 65 receiving testosterone faced a greater risk of myocardial infarction than those younger than 65 on TTh [79]. This finding was consistent with a study by Vigen et al. [80], which also reported an increase in cardiovascular mortality among men with known coronary heart disease when receiving testosterone. Additionally, a randomized, placebo-controlled trial involving men older than 65 years (mean age 74 years) with limited mobility was halted early in 2010 due to a higher incidence of cardiovascular events in the group receiving testosterone compared to the control group [81].

These studies highlight the importance of careful patient selection and monitoring when considering TTh, especially in older men or those with pre-existing cardiovascular conditions. They also underscore the need for more robust research to understand the full scope of the cardiovascular risks and benefits associated with TTh.

The debate over the cardiovascular risks and benefits of TTh is further complicated by contrasting findings from various studies. For instance, a retrospective study [82] and a smaller prospective study [83] in men who received testosterone both reported a reduced risk of cardiovascular mortality compared to those who did not receive testosterone replacement therapy. Moreover, a 3-year prospective study involving

approximately 300 men with subclinical forms of atherosclerosis and risk factors for cardiovascular diseases, with an average age of almost 68 years, did not demonstrate adverse effects on the cardiovascular system [84].

The largest meta-analysis to date, encompassing 35 placebo-controlled studies involving 5601 men, aimed to address concerns about TTh and the risk of cardiovascular events, including arrhythmia, coronary heart disease, heart failure, cerebrovascular events, myocardial infarction, stable angina, peripheral vascular disease, aortic aneurysm, and aortic dissection. This analysis found no evidence of testosterone increasing short- to medium-term cardiovascular risks in men with hypogonadism. However, the long-term safety of testosterone remains less clear, with a lack of data evaluating its long-term impact. Consequently, more long-term studies are needed to fully assess the safety of testosterone therapy [85].

The Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy ResponSE in Hypogonadal Men (TRAVERSE) study is a significant clinical trial designed specifically to measure the time to major adverse cardiovascular events in hypogonadal men at increased risk or with evidence of cardiovascular diseases [86]. This recently published trial reported a non-inferiority of TTh in men with functional hypogonadism and cardiovascular risk factors compared to placebo [87]. The TRAVERSE study was conducted in response to a 2015 request from the US Food and Drug Administration (FDA), which required manufacturers of approved testosterone therapies to conduct clinical studies to determine whether their products were associated with an increased risk of cardiovascular events.

These studies collectively indicate a nuanced and complex relationship between testosterone therapy and cardiovascular health, emphasizing the need for individualized patient assessment and careful consideration of the potential risks and benefits of TTh, especially in men with existing cardiovascular risk factors or diseases.

The TRAVERSE study, a multi-center, randomized, double-blind, placebo-controlled, noninferiority trial, played a crucial role in evaluating the cardiovascular safety of TTh. The study enrolled 5246 men aged 45–80 years who either had preexisting cardiovascular disease or were at high risk for it. These men also reported symptoms of hypogonadism and had two fasting testosterone levels below 300 ng/dL (10.4 nmol/L). Participants were randomly assigned to receive either a daily transdermal 1.62% testosterone gel (with doses adjusted to maintain testosterone levels between 350 ng/dL (12.1 nmol/L) and 750 ng/dL (26.0 nmol/L)) or a placebo gel.

Crucially, this treatment was not associated with an increase in serious cardiovascular events, such as myocardial infarctions or strokes. The primary cardiovascular safety endpoint was the first occurrence of any component of a composite including death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, assessed in a time-to-event analysis. A secondary cardiovascular endpoint included these events plus coronary revascularization. For TTh to be considered noninferior, the upper limit of the 95% confidence interval of the hazard ratio among patients receiving at least one dose of testosterone or placebo had to be less than 1.5. The study found that TTh was non-inferior to placebo with very high significance ($p < .0001$) concerning the incidence of these endpoints, providing initial reassurance regarding the cardiovascular safety of testosterone therapy.

It's important to note that the TRAVERSE study specifically focused on middle-aged or older men with functional hypogonadism and a marked risk profile for cardiovascular disease. Men with classical or severe hypogonadism (testosterone $<$100 ng/dL or 3.4 nmol/L) were excluded from the study. Therefore, the cardiovascular safety results obtained are limited to this specific population and may not be generalizable to all men receiving testosterone therapy, particularly those with more severe forms of hypogonadism.

In the TRAVERSE study, while evaluating the safety and efficacy of TTh, certain adverse events were particularly noted. Among these, atrial fibrillation and unspecified kidney damage were significantly more common in the testosterone group, whereas the incidence of pulmonary embolisms did not show a significant difference between the testosterone and placebo groups. It is important to note that "kidney damage" was not specifically defined in the study, which means this term could cover a range of issues from an increase in serum creatinine levels to kidney trauma, stones, or infections [87].

Regarding the efficacy of TTh, the TRAVERSE trial reported a significantly greater improvement in sexual activity in the testosterone group compared to the placebo group at 6 and 12 months, with this treatment effect being maintained at 24 months. TTh was found to improve hypogonadal symptoms and sexual desire, but not erectile function, in comparison to placebo [88]. This outcome is not entirely unexpected, considering the study population consisted of men with pre-existing cardiovascular disease or a high-risk

profile for such conditions. In such individuals, vascular damage, a contributing factor to erectile dysfunction, is likely to have already been present, potentially limiting the efficacy of TTh in improving erectile function.

These findings from the TRAVERSE study contribute to the nuanced understanding of the benefits and risks associated with TTh, particularly in men with existing cardiovascular conditions or those at high risk. They underscore the importance of a tailored approach when considering TTh, taking into account individual patient profiles and potential risks.

8. Conclusion and clinical Summary

Men with obesity and/or T2D who experience reduced testosterone levels often face a range of associated health challenges. These can include a decrease in muscle mass and strength, diminished vascular reactivity, reduced coronary blood flow, as well as the presence of anemia and hypertension, all of which are linked to increased mortality. In this context, TTh, particularly when combined with lifestyle modifications, has shown multiple clinical benefits.

Clinical and observational studies have demonstrated that TTh can effectively decrease fat mass, improve glucose tolerance, and either prevent or reverse recently diagnosed T2D, along with reducing the risk for cardiovascular adverse events. These

From an epidemiological perspective, the normalization of testosterone concentrations in conjunction with decreased body weight and the improvement or reversal of T2D are associated with favorable cardiometabolic outcomes in men. These findings indicate that TTh could play a significant role in improving overall health outcomes for men with obesity-mediated hypogonadism.

However, from a clinical perspective, while the benefits of TTh are evident, its long-term safety, particularly as a pharmacological strategy for T2D prevention in men with obesity-induced hypogonadism, requires further investigation. This need for additional research underscores the importance of a cautious and individualized approach to TTh, considering both its potential benefits and the need to thoroughly understand its long-term implications on health.

8.1. Clinical relevance: a summary

1. **Functional Hypogonadism and TTh Efficacy:**
   - TTh is effective in improving various metabolic parameters, such as insulin resistance and glycemic control, in men with functional hypogonadism, particularly those with obesity and T2D.
2. **Impact on Cardiovascular Health:**
   - Most studies, including the TRAVERSE trial, show no significant increase in serious cardiovascular events with TTh. Some studies indicate a benefit regarding cardiovascular risk in younger men with metabolic disorders or Type 2 Diabetes Mellitus. The effecs of TTh on Cardiovascular Risk are most likely dependent on baseline conditions and morbidity of hypogonadal patients
3. **Bone Health Improvements:**
   - TTh positively affects bone mineral density, especially in the lumbar spine, in hypogonadal men. It's more effective in younger men and less effective compared to anti-osteoporosis drugs in older men with osteoporosis.
4. **Weight Management and T2D:**
   - TTh, in combination with lifestyle modifications, can lead to significant weight loss, improved muscle mass, and reversal or prevention of recently diagnosed T2D, suggesting its potential role in managing obesity-associated hypogonadism.
5. **Long-Term Safety and Clinical Implications:**
   - While short- to medium-term benefits of TTh are evident, there is a need for more research on its long-term safety, particularly in men with severe hypogonadism or significant cardiovascular risks.

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