REVIEW ARTICLE

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Evaluating the Effects of Testosterone Therapy on Cardiometabolic Health and Well-being in Men with Hypogonadism

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ABSTRACT

Testosterone is crucial for male health, and hypogonadism is prevalent, particularly in men with metabolic comorbidities. While Testosterone Therapy (TTh) is used to manage symptoms, its effects on cardiometabolic health and overall well-being remain debated. This review aimed to synthesize current evidence on the impact of TTh on cardiometabolic parameters, cardiovascular safety, and quality of life in men with hypogonadism. A literature search (2015-2025) across multiple databases identified relevant studies, including Randomized Controlled Trials (RCTs) and observational data, which were narratively synthesized. Results show TTh consistently improves body composition (reduced fat, increased muscle) and aspects of sexual function (libido, activity). However, its effect on glucose metabolism remains controversial, with conflicting findings. While large RCTs indicate no increased risk of major adverse cardiovascular events over the medium term, TTh is associated with increased specific risks including pulmonary embolism, atrial fibrillation, acute kidney injury, and polycythemia. Benefits on mood/energy are modest, and effects on other quality of life domains are limited. In conclusion, TTh offers clear benefits for body composition and sexual function. Clinicians must balance these with controversial glucose effects and increased specific adverse event risks, requiring careful patient selection and monitoring. Further long-term research is needed.

Keywords: Testosterone therapy, hypogonadism, cardiometabolic health, quality of life, adverse cardiovascular events

INTRODUCTION

Testosterone is the principal androgen hormone in men, playing a central role in the regulation of male sexual differentiation, the development and maintenance of secondary sexual characteristics, spermatogenesis, and fertility.[1] Beyond its well-established reproductive functions, testosterone exerts widespread effects on numerous physiological systems. It is a key modulator of body composition, promoting muscle mass, reducing fat mass, and influences glucose and lipid metabolism, thereby contributing significantly to overall metabolic health.[2] Moreover, adequate testosterone levels are associated with cardiovascular health, as low testosterone has been linked to increased cardiovascular risk factors, including insulin resistance, dyslipidemia, hypertension, and

visceral adiposity.[3] Testosterone is also involved in various neuropsychological processes, contributing to mood regulation, energy levels, cognitive function, and general well-being, highlighting its systemic importance.

Physiologically, testosterone levels decline gradually with advancing age, in a process commonly referred to as late-onset hypogonadism or age-related testosterone deficiency. This age-related decline is often compounded by comorbid conditions such as obesity, type 2 diabetes mellitus (T2D), metabolic syndrome (MetS), and chronic illnesses, as well as by lifestyle factors, certain medications, and genetic predispositions.[4] A substantial proportion of men with these metabolic comorbidities exhibit low testosterone levels, with estimates suggesting that up to 50% of obese men or those with T2D or MetS are affected.[5,6] The relationship between testosterone and adiposity is complex and bidirectional: increased visceral fat leads to higher aromatase activity and conversion of testosterone to estradiol, suppressing the hypothalamic-pituitary-gonadal axis, while testosterone deficiency itself contributes to fat accumulation and metabolic derangements.[7] Similarly, men with MetS, characterized by central obesity, hyperglycemia, insulin resistance, hypertension, and dyslipidemia, often exhibit significantly lower testosterone concentrations compared to metabolically healthy individuals.[8] In light of testosterone's diverse physiological roles and the high prevalence of hypogonadism among men with metabolic disorders, testosterone therapy (TTh) has gained substantial attention as a potential therapeutic strategy. The primary aim of TTh is to restore serum testosterone levels to a physiological range to alleviate symptoms of hypogonadism, such as sexual dysfunction, low energy, depressive symptoms, and loss of muscle mass. However, the potential benefits of TTh extend beyond symptomatic relief, with growing interest in its metabolic and cardiovascular effects. Several clinical studies and observational reports have suggested that TTh may enhance insulin sensitivity, lower fasting glucose and glycated hemoglobin (HbA1c), improve lipid profiles by reducing total cholesterol and triglycerides, and favorably influence body composition by decreasing fat mass and increasing lean mass.[4,9] These findings indicate that TTh may offer cardiometabolic benefits, particularly for men with comorbid conditions such as T2D or MetS. Nonetheless, the safety of TTh remains controversial, as some reports have raised concerns about increased cardiovascular risk, especially in older men or those with underlying cardiovascular disease. Additionally, TTh can lead to increased hematocrit levels, raising concerns about the risk of erythrocytosis and venous thromboembolism.[10]

Given these potential benefits and risks, there is a critical need for a comprehensive and balanced synthesis of the current literature to guide clinical practice. This review aims to evaluate the most recent and robust evidence regarding the effects of testosterone therapy in men with hypogonadism, with a specific focus on its impact on cardiometabolic health (including metabolic parameters, cardiovascular outcomes, and safety considerations) as well as on broader quality-of-life measures such as sexual function, mood, and vitality. Additionally, this review seeks to identify gaps in the existing body of research and highlight areas where further investigation is warranted, particularly in high-risk populations and long-term therapeutic contexts.

METHODOLOGY

The authors conducted a literature search across databases such as PubMed, Scopus, ProQuest, EBSCO, and Google Scholar to identify studies related to the use of therapy TTh and its impact on cardiometabolic health in men, with a publication date range from 2015 to 2025. The search was performed using Boolean

operators with keywords such as (“testosterone therapy” OR “testosterone replacement therapy” OR “TTh” OR “TRT”) AND (“cardiometabolic health” OR “cardiovascular risk” OR “metabolic syndrome” OR “insulin resistance”).

All authors conducted an initial screening of titles and abstracts obtained electronically, followed by independent assessment of the full texts of studies that potentially met the inclusion criteria. Inclusion criteria encompassed observational studies, randomized controlled trials (RCTs), meta-analyses, and systematic reviews that evaluated the effects of testosterone therapy on cardiometabolic health parameters (such as insulin resistance, blood glucose levels, lipid profiles, body composition, cardiovascular events, and related safety) and/or quality of life outcomes (such as sexual function, mood, and energy levels) in men. Only studies with complete data available in either Indonesian or English were included.

Data extracted from each study meeting the inclusion criteria included study characteristics (e.g., study design), participant population characteristics (including age and comorbid conditions), details of the testosterone therapy protocol (including dosage, route of administration, and duration of therapy), relevant outcomes (metabolic parameters, cardiovascular events, adverse effects, and quality-of-life indicators), and other key findings. All extracted data were then synthesized and reported narratively in the Results and Discussion section. Any disagreements that arose among the authors during the screening, full-text assessment, or data extraction processes were resolved through discussion until consensus was reached.

RESULT

Study Characteristics

A summary of the study characteristics is presented in Table 1. A total of 13 studies from various literature sources were included, consisting of diverse study designs, including RCTs and longitudinal observational studies. The interventions examined involved the use of TTh in various formulations (intramuscular injections, transdermal gels, and subcutaneous pellets) with differing doses and durations.

These studies involved male participants with hypogonadism, which in many cases was associated with metabolic comorbidities such as type T2D, MetS, and obesity. Participant ages varied widely, although most were from the middle-aged to elderly groups. The relationship between hypogonadism and metabolic comorbidities is bidirectional, with hypogonadism potentially being either a cause or consequence of these conditions. Two studies included men with various health conditions without specific criteria related to hypogonadism or comorbidities, while one study specifically involved hypogonadal men with cardiovascular risk.

Despite disparities in the types of testosterone preparations, dosing regimens, administration routes, baseline comorbidities, and testosterone levels across studies, these parameters were still generally comparable. Key clinical outcomes such as changes in body composition, metabolic parameters, sexual function, and major cardiovascular events remained objective parameters that could be assessed statistically.

Cardiometabolic and Functional Implications of Testosterone Deficiency

Testosterone deficiency in men is associated with a range of adverse health outcomes, affecting metabolic processes, cardiovascular health, and overall quality of life. The decline of this crucial hormone triggers a cascade of interconnected physiological changes that can significantly impair well-being.

Table 1. Study characteristics.

Author (Year)	Country	Study Design	Intervention	Population	Age (years)	Sample Size (n)	Formulation	Dose	Follow-up Duration
Malyar Emranian (2015)	US	Case-Ctrl Study	TTh	Various men	70.4 (case), 71.0 (control)	934,243	Various (injection, gel, patch, oral)	N/A	N/A
Geoffrey Hackett (2019)	UK	Longit Obs Cohort	TTh	Men w/ T2D & Hypog	Avg 64.6 yrs	857	Various	1000 mg	N/A
Christopher J.D Wallis (2016)	Canada	Pop-Based Retro Cohort	TTh	Various men	≥66 yrs	10,311 (TTh) vs 28,029 (control)	All T formulations	N/A	63.6 months
Jemma Hudson (2022)	Global	MA (RCT, IPD)	TTh	Men w/ Hypog	≥18 yrs (avg 65)	5601	All T formulations	Varies	Varies across studies
Yuliya Tishova (2024)	Russia	DB PC RCT	TTh	Men w/ MetS & Hypog	35–70 yrs	184	Parenteral TU	1000 mg	34.5 months
Aksam Yassin (2019)	Germany, UAE	LT Obs Registry	TTh	Men w/ preDM & Hypog	Avg 61.5 (TTh), 61.6 (control)	319	Parenteral TU	1000 mg	126 months
Karim Sultan Haider (2020)	Germany, UAE	LT Obs Registry	TTh	Men w/ preDM & Hypog	Avg 51.5–54.4 (TTh), 53.7–54.9 (control)	356	Parenteral TU	1000 mg	132 months
Gary Wittert (2021)	Australia	DB PC Phase 3b RCT	TTh + lifestyle intervention	Obese/ overweight men w/ low T or T2D	56.1–56.5 yrs	1007	Parenteral TU	1000 mg	24 months
Shalender Bhasin (2024)	US	PC RCT Substudy	TTh	Men w/ Hypog + preDM/DM	68.8 ± 1.9 yrs	5204	T gel	1.62%	48 months
A.M. Lincoff (2023)	US	Multicenter DB RCT	TTh	Men w/ Hypog + preDM/DM	63.3–77.9 yrs	5204	T gel	1.62%	Avg 3.2 yrs
Karol M. Pencina (2023)	US	DB RCT Substudy	TTh	Men w/ Hypog + CV risk	63.7 (7.6) yrs	1161	T gel	1.62%	Avg 3.3 yrs
Shalender Bhasin (2024)	US	Noninferiority RCT Substudy + Phase 4	TTh	Men w/ Hypog + preDM/DM	45–80 yrs	2643	T gel	1.62%	Avg 3.2 yrs
Mathis Grossmann (2024)	Australia	Secondary analysis of T4DM Trial	TTh + lifestyle intervention	Obese/ overweight men w/ low T/T2D	Avg 56.0 yrs	648	Parenteral TU	1000 mg	24 months

Avg: Average, Case-Ctrl Study: Case-Control Study, CV: Cardiovascular, DB: Double-Blind, DM: Diabetes Mellitus, Hypog: Hypogonadism, IPD: Individual Participant Data, LT Obs Registry: Long-term Observational Registry, Longit Obs Cohort: Longitudinal Observational Cohort, MA: Meta-Analysis, MetS: Metabolic Syndrome, N/A: Not Available, PC: Placebo-Controlled, Pop-Based Retro Cohort: Population-Based Retrospective Cohort, preDM: Prediabetes, RCT: Randomized Controlled Trial, Retro: Retrospective, T gel: Testosterone gel, TTh: Testosterone Therapy, TU: Testosteron undecanoat, T2D: Type 2 Diabetes, US: United States, UK: United Kingdom, w/: with, yrs: years.

Metabolic implications

Testosterone deficiency significantly disrupts metabolic homeostasis, primarily by reducing insulin sensitivity and altering lipid profiles, while also contributing to a bidirectional negative relationship with obesity. Low testosterone levels impair the body's ability to respond to insulin through several key mechanisms. A decrease in Glucose Transporter Type (GLUT4) expression in skeletal muscle and subcutaneous adipose tissue limits glucose uptake, while disturbances in insulin signaling pathways further worsen glucose control and glycogen synthesis. In adipose tissue, heightened activity of inflammatory pathways promotes the release of pro-inflammatory cytokines such as Interleukin-6

(IL-6) and Monocyte Chemoattractant Protein-1 (MCP-1), which further impair insulin function and exacerbate metabolic dysfunction. In the liver, increased regulation of lipogenic enzymes drives fat accumulation (steatosis), further contributing to systemic insulin resistance.[11–13]

Testosterone deficiency also adversely affects lipid metabolism, resulting in an atherogenic lipid profile. Reduced activity of lipoprotein lipase (LPL) hinders triglyceride clearance, while increased release of free fatty acids from visceral adipose tissue prompts the liver to produce more triglycerides. Enhanced hepatic lipogenesis leads to greater secretion of VLDL-TG, worsening dyslipidemia. Moreover, low testosterone levels reduce HDL cholesterol by disrupting the expression of key proteins involved in reverse cholesterol transport. Dysregulation of nuclear receptor signaling pathways associated with lipid metabolism further exacerbates this imbalance.[11]

The relationship between testosterone deficiency and obesity is bidirectional and forms a vicious cycle. Obesity reduces testosterone levels through several mechanisms, including increased aromatase activity in visceral fat tissue, which converts testosterone into estradiol and suppresses the hypothalamic-pituitary-testicular axis. Additionally, the release of pro-inflammatory cytokines such as Tumor Necrosis Factor-alpha and IL-6 from visceral fat disrupts hormonal signaling to the testes. Insulin resistance and hyperinsulinemia associated with obesity lower the production of sex hormone-binding globulin, reducing total testosterone levels. Changes in adipokine levels also play a role: hyperleptinemia leads to leptin resistance, reducing hypothalamic hormonal stimulation, while decreased adiponectin impairs Leydig cell function in testosterone production.[9,14–16]

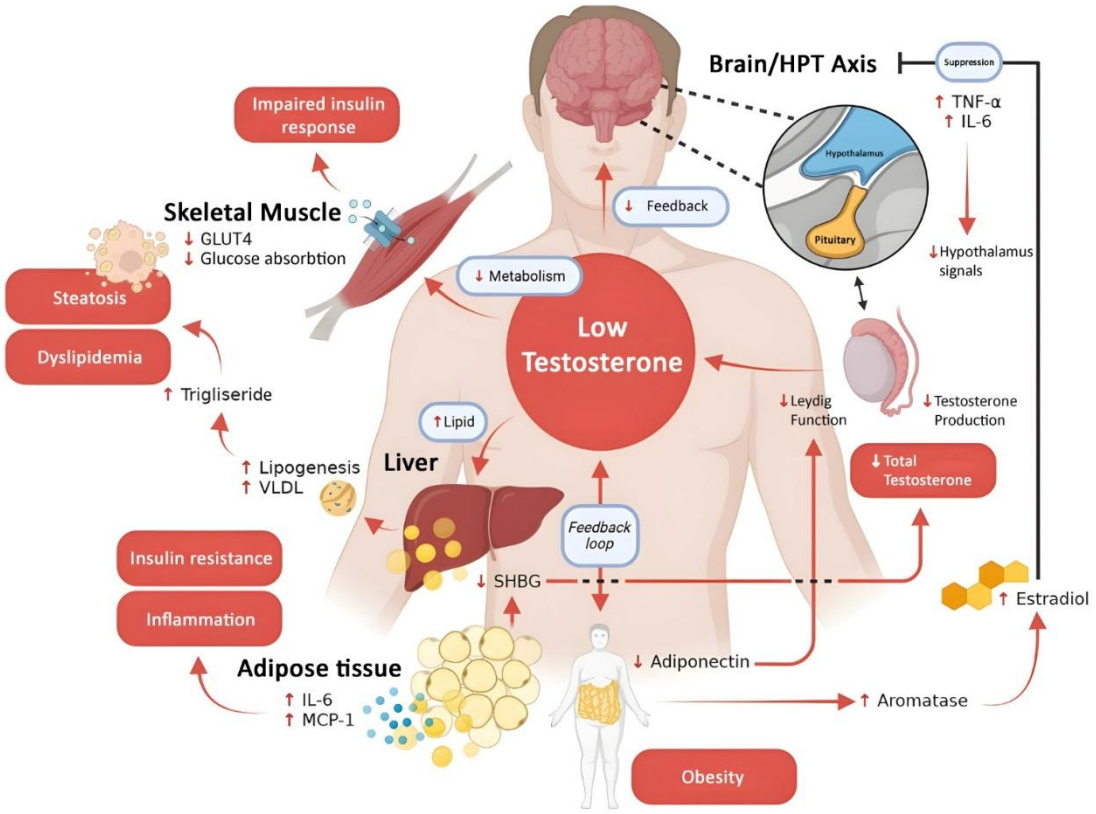

Figure 1. Multifactorial interactions between testosterone deficiency and metabolic disorders.

Conversely, low testosterone actively promotes the development of obesity by triggering fat accumulation and disrupting lipid metabolism. Testosterone plays a critical role in regulating body composition by suppressing the formation of adipocytes, particularly in visceral tissue. When testosterone levels are low, this process is impaired, making preadipocytes more likely to differentiate into mature fat cells. Additionally, low testosterone increases triglyceride uptake into adipose tissue and reduces the body's ability to break down and burn fat due to decreased activity of key enzymes involved in lipolysis and fat oxidation. These disturbances are compounded by the loss of lean muscle mass, which is a major site of energy metabolism. Clinically, low testosterone levels are a strong predictor of increased visceral fat over time.[9,15–17]

Cardiovascular implications

Testosterone deficiency has detrimental effects on the cardiovascular system, primarily by triggering endothelial dysfunction and creating a pro-inflammatory vascular environment. One of the key mechanisms is the reduced bioavailability of nitric oxide (NO), a vital vasodilator produced by the enzyme endothelial nitric oxide synthase (eNOS). Low testosterone levels decrease eNOS activity and increase oxidative stress, which further suppresses NO production and generates reactive oxygen species that can damage endothelial cells directly or by inactivating NO. In addition, low testosterone levels promote increased synthesis of endothelin-1 (ET-1), a potent vasoconstrictor, disrupting the balance between NO and ET-1 and worsening vascular dysfunction. This condition is also accompanied by elevated levels of adhesion molecules such as vascular cell adhesion molecule-1 and increased leukocyte–endothelium interactions, which indicate vascular inflammatory activation. This pro-inflammatory status is further evidenced by elevated levels of systemic inflammatory markers such as high-sensitivity C-reactive protein (hs-CRP) and TNF-α, as supported by findings in animal models. This feed-forward loop of inflammation is exacerbated by cytokines like IL-6 and TNF-α, which upregulate the expression of adhesion molecules and reinforce vascular damage.[18–21]

Quality of life implications

One of the most prominent effects of low testosterone is a decline in sexual function, which can significantly reduce quality of life. Clinically, this often manifests as erectile dysfunction, decreased sexual desire hypoactive sexual desire disorder, or delayed ejaculation. These issues rarely occur in isolation; they are frequently associated with systemic health conditions and an increased risk of mortality, making them an important indicator of overall male well-being.[22]

Table 2. Cardiovascular implications of testosterone deficiency

Mechanism	Effect of Testosterone Deficiency	Cardiovascular Impact
Endothelial Function	↓ eNOS Activity, ↑ Oxidative Stress	↓ Nitric Oxide (NO), Endothelial Dysfunction
Vascular Tone Regulation	↑ Endothelin-1 (ET-1), ↓ NO	Vasoconstriction, ↑ Vascular Resistance
Inflammatory Markers	↑ hs-CRP, TNF-α, IL-6	Chronic Vascular Inflammation
Cellular Adhesion Molecules	↑ VCAM-1, ↑ Leukocyte interaction with Endothelium	Atherosclerosis worsening
Forward Inflammation Loop	Cytokines amplify Oxidative Stress and Endothelial Damage	Progressive Vascular Damage

eNOS: Endothelial Nitric Oxide Synthase, ET-1: Endothelin-1, hs-CRP: High-Sensitivity C-Reactive Protein, IL-6: Interleukin-6, NO: Nitric Oxide, TNF-α: Tumor Necrosis Factor alpha, VCAM-1: Vascular Cell Adhesion Molecule-1, ↑: Increased/Elevated, ↓: Decreased/Reduced.

Table 3. Implications of testosterone deficiency for quality of life

Aspect	Specific Effect	Impact
Sexual Function	**↓ Libido, ED, Delayed Ejaculation**	**Decreased sexual satisfaction, ↓ Self-Esteem**
Mood & Emotion	↑ Depression, fatigue, irritability, ↓ vitality and motivation	Impaired daily activities and social relations
Cognition & Behavior	↓ Drive for dominance, ↓ assertiveness, impaired stress response	Impaired work performance, impaired decision-making
Neurobiological	Neurotransmitter and brain plasticity impairment	↓ Psychological resilience
Genetic Factors	Variation in CAG repeat length in androgen receptor affects hormone sensitivity	Symptom and treatment response variability

CAG: Cytosine-Adenine-Guanine, ED: Erectile Dysfunction, ↑: Increased/Elevated, ↓: Decreased/Reduced.

Beyond sexual health, low testosterone also affects psychological and behavioral aspects. Men with testosterone deficiency are more susceptible to dysphoria, chronic fatigue, irritability, decreased vitality and assertiveness, and even depression. Testosterone functions as a neuroactive steroid, influencing neurotransmitters, brain plasticity, and the modulation of stress and emotional responses. These symptoms can profoundly affect daily life, but TTh has been shown to improve energy levels, mood, and vitality. This hormone also plays a role in motivated behaviors such as dominance and status-seeking, which can influence self-perception and social interactions. These effects may also be modulated by genetic factors, such as the length of coronary angiography repeats in the androgen receptor gene, which can alter hormonal sensitivity in the brain.[23]

Effects of Testosterone Therapy on Metabolic Parameters

TTh has demonstrated various effects on metabolic parameters in men, particularly those with hypogonadism, prediabetes, type 2 diabetes (T2D), or metabolic syndrome (MetS), as shown in multiple studies. Several investigations have highlighted its potential benefits on glucose metabolism.

One study involving men participating in a lifestyle program found that TTh significantly reduced the incidence of T2D over two years compared to placebo (12% vs. 21%) and led to greater improvements in 2-hour glucose levels after an oral glucose tolerance test (OGTT).[24] Similarly, an eight-year registry study reported that long-term TTh in hypogonadal men with prediabetes prevented progression to T2D, with 90% achieving normal glucose regulation (HbA1c <5.7%), compared to 40.2% who progressed in the untreated control group. This study also noted improvements in fasting glucose and HbA1c following TTh administration.[25] Furthermore, an eleven-year registry study observed T2D remission (defined as HbA1c <6.5% without medication) in 34.3% of hypogonadal men with T2D receiving TTh, along with significant and sustained reductions in fasting glucose and HbA1c levels, changes not observed in the control group.[26]

Improved insulin sensitivity has also been reported. TTh significantly reduced homeostatic model assessment of insulin resistance (HOMA-IR) (a marker of insulin resistance) from baseline in hypogonadal men with MetS, primarily by lowering fasting insulin levels more than fasting glucose levels.[27] The eleven-year registry study also documented significant reductions in fasting insulin and HOMA-IR in the TTh group, indicating improved insulin sensitivity, while these markers worsened in the control group.[26] Additionally, the triglyceride-glucose index and lipid accumulation product also declined with TTh in the eight-year registry study.[25]

However, not all studies support TTh's role in glycemic control or diabetes prevention. A major substudy from the TRAVERSE RCTs found no

difference between TTh and placebo in the risk of progression from prediabetes to T2D over up to 48 months. This study also did not show significant increases in glycemic remission rates among men with existing diabetes, nor improvements in fasting glucose or HbA1c levels compared to placebo in middle-aged and older men with hypogonadism.[28] Supporting these findings, a study by Wittert et al. (2021), despite showing benefits for T2D incidence and OGTT glucose, found no significant difference in HbA1c changes between the TTh and placebo groups over two years.[24]

Regarding body composition and anthropometric parameters, the findings generally indicate improvements with TTh. Studies consistently reported greater reductions in waist circumference in men receiving TTh compared to controls or placebo.[24–27] Weight loss and reductions in body mass index (BMI) were also observed in long-term registry studies.[25,26] Moreover, TTh was associated with greater reductions in total fat mass and abdominal fat mass, along with increases in total muscle mass and arm muscle mass. This shift from fat mass to lean mass may explain why overall weight loss is not always significant, as seen in the Wittert et al. (2021) study, where fat loss was offset by gains in muscle mass.[24]

Improvements in lipid profiles have also been reported, particularly in long-term registry studies. TTh was associated with significant improvements in total cholesterol, Low-Density Lipoprotein (LDL), High-Density Lipoprotein (HDL), triglycerides, triglyceride-to-HDL ratio, and non-HDL cholesterol compared to untreated controls.[25,26] Remnant cholesterol levels also declined significantly with TTh in the eleven-year registry study.[26]

Effects of Testosterone Therapy on Cardiovascular Risk

The cardiovascular safety profile of (TTh) presents a complex picture, with recent large-scale trials offering valuable insights, alongside findings from observational studies and meta-analyses. The key result from the TRAVERSE RCTs, which involved middle-aged and older men with hypogonadism and high cardiovascular risk, was that TTh was non-inferior to placebo in terms of major adverse cardiac events (MACE)—a composite outcome of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. The incidence of first MACE events was similar between the TTh group (7.0%) and the placebo group (7.3%) over an average follow-up period of about three years.[29] This finding aligns with results from a meta-analysis that found no evidence that TTh increased the overall risk of cardiovascular or cerebrovascular events compared to placebo in the short- to medium-term (mean follow-up of 9.5 months), with comparable event rates (7.5% in TTh vs. 7.2% in placebo).[30] Furthermore, a large pharmacoepidemiological study focusing on myocardial infarction did not find any statistically significant association between either current or past use of TTh and myocardial infarction risk.[31] Regarding mortality, some observational evidence suggests potential benefits of TTh. A study in men with T2D and low testosterone levels found that TTh was associated with a significant reduction in all-cause mortality compared to untreated men, particularly among older individuals or those who were less overweight, despite no improvements in conventional cardiovascular risk factors such as lipid profiles or blood pressure.[30] Another observational cohort study also showed that TTh use overall was linked to lower mortality, with the effect strongly dependent on the duration of therapy; long-term use (>35 months) was associated with a significantly reduced risk of death compared to controls.[32] However, in meta-analyses, although fewer deaths were observed in the TTh group (0.4% vs. 0.8%), this difference did not reach statistical significance, likely due to the short

duration of follow-up and low event rates in the analyzed trials.[30]

The timing and duration of TTh exposure may influence cardiovascular risk, although most findings derive from observational data that are prone to bias. One cohort study reported that short-term exposure to TTh (median of 2 months) was associated with increased mortality and cardiovascular events, whereas long-term exposure (median of 35 months) was associated with reduced risk for both outcomes compared to controls.[32] Similarly, a pharmacoepidemiological study found a small but statistically significant increased risk of myocardial infarction in new users of TTh (within the first 90 days of therapy), a risk not observed in long-term users. The absolute increase in risk was considered low (Number Needed to Harm, 305).[31] These findings suggest a potential early hazard or risk with short-term use, which contrasts with the possible benefits of long-term use. However, interpreting these results requires caution while awaiting confirmation from more robust RCTs.

Although the TRAVERSE trial did not find an increased risk of MACE, it did identify higher incidences of certain specific adverse events in the TTh group compared to placebo. Notably, there was a higher incidence of pulmonary embolism (0.9% vs. 0.5%), atrial fibrillation (3.5% vs. 2.4% as reported by investigators; 5.2% vs. 3.3% for nonfatal arrhythmic events requiring intervention after adjudication), and acute kidney injury (2.3% vs. 1.5% per investigator report) in the TTh group.[29] In line with known physiological effects, meta-analyses also reported a significant increase in hematocrit/hemoglobin levels (leading to higher rates of polycythemia) and a greater incidence of edema in the TTh group, although no overall increase in venous thromboembolism events was observed in the short- to medium-term data analyzed.[30]

Effects of Testosterone Therapy on Quality of Life

TTh demonstrates specific, though not universal, benefits on aspects of quality of life (QoL) in men with hypogonadism. The most consistently reported improvements are found in the domain of sexual function. One study found that TTh significantly enhanced overall sexual activity and sexual desire (libido) compared to placebo in middle-aged and older men with hypogonadism, with these positive effects sustained over a 2-year period.[33] This improvement in sexual well-being was accompanied by a significant reduction in the overall burden of hypogonadism symptoms, as measured by the Hypogonadism Impact of Symptoms Questionnaire (HIS-Q), indicating broader symptom relief.[33] However, it is important to note that the same study did not find a significant difference between TTh and placebo in the improvement of erectile function scores (IIEF-5).[33]

Regarding mood and energy levels, evidence shows mild improvements with TTh. A sub-study of the TRAVERSE trial reported a small but statistically significant increase in mood and energy compared to placebo, particularly evident in men who had depressive symptoms at baseline.[34] However, the positive impact on mood appeared limited, primarily benefiting men with mild to moderate depressive symptoms (baseline PHQ-9 scores between 5–14), and showing no significant advantage over placebo in those with moderate to severe depression.[34] Based on these findings, TTh is generally not considered a primary treatment for clinical depressive disorders.[34]

TTh benefits appear less evident or absent in other QoL domains. Studies using HIS-Q domains did not find significant improvements attributable to TTh in perceived cognitive function or sleep quality compared to placebo.[28] Moreover, in a 2-year trial involving overweight or obese men

participating in a lifestyle modification program, TTh did not produce consistent improvements in broader health-related QOL(HR-QOL) measures, such as the physical and mental component scores of the SF-12, or in psychosocial function indicators like personal mastery and subjective social status relative to society, when compared with placebo. Although temporary improvements in self-cohesion and relative social status among peers were observed midway through the study, these effects did not persist until the end of the study.[35]

Interestingly, other factors such as lifestyle changes may have a greater impact on QoL than TTh in certain populations. The study by Grossmann et al. (2024) clearly demonstrated that weight loss achieved through accompanying lifestyle interventions significantly improved mental quality of life, personal mastery, and subjective social status, indicating that weight management exerted a more positive influence on these aspects than TTh alone in overweight or obese men. This study also highlighted that better baseline psychosocial health predicted greater success in weight loss programs.[35]

DISCUSSION

This literature review aimed to evaluate the current evidence regarding the impact of (TTh) on cardiometabolic health and overall well-being in men with hypogonadism. Analysis of relevant studies highlights the complexity of TTh effects, with findings varying depending on the measured parameters, study design, and population characteristics. Physiologically, testosterone plays a critical role in regulating glucose and lipid metabolism, body composition, and cardiovascular function, providing a biological rationale for the expected cardiometabolic benefits of TTh in men with hormone deficiency. However, clinical evidence presents a more nuanced picture.

In terms of metabolic parameters, TTh consistently shows benefits on body composition, with significant reductions in waist circumference, fat mass (particularly abdominal fat), and increases in muscle mass reported across various studies, including clinical trials and long-term registry studies.[24–27] Positive effects on lipid profiles, such as improvements in total cholesterol, LDL, HDL, and triglycerides compared to controls, have also been reported in long-term registry data.[25,26] However, the impact of TTh on glucose metabolism remains a subject of debate. While some observational and long-term registry studies suggest TTh may help prevent progression to T2D, induce T2D remission, and improve glycemic control and insulin sensitivity,[24–27] large-scale RCTs, such as the TRAVERSE substudy, found no significant benefit of TTh over placebo in terms of diabetes progression, glycemic remission, or improvements in HbA1c and fasting glucose over a follow-up period of up to 48 months.[28] These differing results may be attributed to variations in methodology, follow-up duration, or population characteristics across studies, highlighting the need for further research to clarify the role of TTh in glycemic management.

Regarding safety and cardiovascular risk, the TRAVERSE RCT provides important evidence that TTh is not inferior to placebo in terms of MACE in middle-aged and older men with hypogonadism and high cardiovascular risk over approximately three years.[29] This finding is supported by meta-analyses and pharmacoepidemiologic studies that also found no overall increase in MACE risk.[30,31] Some observational studies even suggest a potential reduction in mortality with long-term TTh use,[32,36] although short-term trial meta-analyses did not find statistically significant differences in mortality rates.[30] Nevertheless, the safety profile of TTh is not without concerns. The TRAVERSE trial identified increased incidences of venous

thromboembolism (particularly pulmonary embolism), atrial fibrillation, and acute kidney injury in the TTh group.[29] Increases in hematocrit and hemoglobin, leading to heightened risks of polycythemia and edema, are also known and confirmed side effects.[30] Observational data suggesting a potential elevation in cardiovascular risk during early or short-term therapy warrant further confirmation through RCTs.[31,32]

Assessment of TTh's impact on well-being and quality of life indicates benefits primarily in the domain of sexual function. TTh has been consistently reported to improve overall sexual activity and sexual desire (libido), and to reduce the symptom burden of hypogonadism.[33] However, these benefits do not extend to improvements in erectile function as measured by IIEF-5.[33] There is also evidence of small but statistically significant improvements in mood and energy levels, especially among men with mild to moderate depressive symptoms at baseline,[34] although TTh is not indicated as a primary therapy for clinical depression. TTh appears to offer little or no benefit in other quality-of-life domains, such as perceived cognitive function, sleep quality, or broader HR-QOL measures.[34,35] Interestingly, in overweight or obese men, lifestyle interventions such as weight loss have shown a greater impact on mental and psychosocial quality of life than TTh alone.[35]

While the TRAVERSE trial provides compelling evidence regarding the cardiovascular safety of TTh, some experts have expressed nuanced perspectives that merit consideration. Khera et al. acknowledged the trial's significance in advancing testosterone research and providing valuable safety and efficacy insights.[37] However, Krishnan et al. cautioned against overly simplistic interpretations for real-world application, citing limitations such as high discontinuation rates and short treatment duration.[38] Budoff further emphasized trial shortcomings, including early termination and inadequate testosterone restoration, which could create a false sense of security.[39] Despite these concerns, Hackett and Ramachandran suggested that the positive findings may justify the relaxation of cardiovascular warnings on testosterone products.[40] These differing viewpoints underscore the ongoing debate about balancing the observed benefits of TTh, particularly in enhancing sexual function and libido, with the need for careful interpretation of safety data and awareness of potential risks.

CONCLUSION

In conclusion, this review synthesizes current evidence on the impact of (TTh) on cardiometabolic health and overall well-being in men with hypogonadism, highlighting a complex picture. TTh consistently demonstrates benefits in body composition (reduction in fat mass, increase in muscle mass) and sexual function, particularly in libido and sexual activity. However, its effects on glycemic control remain controversial, with conflicting findings between observational studies and large clinical trials, indicating the need for further research.

In terms of cardiovascular safety, trials such as TRAVERSE show that TTh is non-inferior to placebo for MACE, but they also indicate increased risks of specific adverse events, including venous thromboembolism, atrial fibrillation, acute kidney injury, and polycythemia. The benefits of TTh on mood and energy are moderate, while its impact on other aspects of quality of life is limited.

Therefore, while TTh offers meaningful benefits, careful consideration of its risk-benefit profile remains essential. Research gaps that need to be addressed include confirmation of long-term safety, clarification of its precise role in glycemic management, understanding the mechanisms behind specific adverse effects, evaluating effectiveness in particular subpopulations, and assessing quality of life using

appropriate instruments. This body of evidence is crucial to support more personalized clinical decision-making for men with hypogonadism.

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