REVIEW

OPEN

Testosterone and weight loss: the evidence

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Purpose of review

The purpose of this article is to examine the contemporary data linking testosterone therapy in overweight and obese men with testosterone deficiency to increased lean body mass, decreased fat mass, improvement in overall body composition and sustained weight loss. This is of paramount importance because testosterone therapy in obese men with testosterone deficiency represents a novel and a timely therapeutic strategy for managing obesity in men with testosterone deficiency.

Recent findings

Long-term testosterone therapy in men with testosterone deficiency produces significant and sustained weight loss, marked reduction in waist circumference and BMI and improvement in body composition. Further, testosterone therapy ameliorates components of the metabolic syndrome. The aforementioned improvements are attributed to improved mitochondrial function, increased energy utilization, increased motivation and vigor resulting in improved cardio-metabolic function and enhanced physical activity.

Summary

The implication of testosterone therapy in management of obesity in men with testosterone deficiency is of paramount clinical significance, as it produces sustained weight loss without recidivism. On the contrary, alternative therapeutic approaches other than bariatric surgery failed to produce significant and sustained outcome and exhibit a high rate of recidivism. These findings represent strong foundations for testosterone therapy in obese men with testosterone deficiency and should spur clinical research for better understanding of usefulness of testosterone therapy in treatment of underlying pathophysiological conditions of obesity.

Keywords

BMI, obesity, testosterone therapy, waist circumference, weight loss

INTRODUCTION

Obesity impacts quality of life and shortens life expectancy. Obesity is a chronic condition that cannot be ameliorated simply with lifestyle behavior alone [1,2]. Obesity contributes to insulin resistance, type 2 diabetes (T2DM) and is associated with a host of comorbidities and therefore represents a healthcare crisis. Lifestyle changes produce modest weight loss in the early stages of weight management strategies, but a high rate of recidivism is observed. Treatment of obesity necessitates evidence-based medical interventions [3,4]. Although lifestyle modifications are highly recommended, as integral part of strategies designed for treatment and management of obesity [5–7], in most patients, such strategies are not always successful in the long term because of high rate of recidivism, in part due to lack of adherence to prescribed regimen [8–11]. The limited benefits of the current approved drugs, together with the undesirable adverse side-effects of such agents in long-term management of obesity have contributed to reduced adherence rates and to discontinuation of use [2]. Efforts to target patient education and increase awareness are warranted.

Desirable outcomes in management of overweight and obesity necessitates development and utilization of new well tolerated and efficacious agents, which can be used in combination with lifestyle changes to achieve weight loss. Contemporary approaches to management of obesity include lifestyle modifications [12] and pharmaco-therapeutic agents, such as incretin and glucagon-like

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KEY POINTS

- Long-term testosterone therapy in men with testosterone deficiency improves body composition and quality of life.
- Long-term testosterone therapy in obese men with testosterone deficiency ameliorates all metabolic syndrome (MetS) components.
- Long-term testosterone therapy in men with testosterone deficiency, with or without lifestyle modifications, may prove very effective and useful in the management of obesity.

peptide-1 (GLP-1) receptor agonists [13], enzyme inhibitors (dipeptidyl peptidase inhibitors) [14], angiopoietin-like proteins [15] and bariatric surgery [16]. Furthermore, a number of Food and Drug Administration (FDA)-approved drugs for treatment of obesity have serious adverse side-effects and were taken off the market [12,17]. Thus, limited approaches to manage obesity are available except lifestyle changes, which produce moderate effects on weight loss and in most cases are unsustainable. Here, we summarize recent findings related to long-term testosterone therapy that produces improvement in body composition and more specifically weight loss, reduction in waist circumference and BMI. We propose use of testosterone therapy as a new strategy for managing overweight and obesity in men with testosterone deficiency.

CLINICAL CHALLENGES IN MANAGEMENT OF OBESITY

Clinicians face complex challenges in their fight to treat and manage obesity. These include a lack of well tolerated and effective pharmaco-therapeutic agents and patients monitoring to safeguard against serious adverse side-effects. Further, FDA-approved pharmaco-therapeutic agents offer only modest benefits in some but not all patients. A more difficult challenge is patients' adherence and compliance and the perceived moderate effects and the undesirable adverse side-effects that contribute to the limited utility of the available drugs [2]. A number of centrally acting drugs intended to regulate appetite were employed, however, agents, such as fenfluramine, dexfenfluramine, sibutramine, venlafaxine, rimonabant, phentermine diethylpropion; phendimetrazine and benzphentamine, were withdrawn from the market because of adverse side-effects or lack of efficacy in treatment of obesity [2].

NEW APPROACHES FOR TREATMENT OF OBESITY IN MEN WITH TESTOSTERONE DEFICIENCY (HYPOGONADISM)

The prevalence of testosterone deficiency increases with comorbidities, such as insulin resistance and T2DM, obesity, hypertension, and cardiovascular disease (CVD) ranging from 30 to 50% [18–21]. Mulligan *et al.* [18] reported that approximately 52.4% of all obese men had testosterone levels below 300 ng/dl (10.4 nmol/l). Similarly, Luconi *et al.* [22] suggested that approximately 75% of men with obesity grade III awaiting bariatric surgery had hypogonadism. In our study of 255 hypogonadal men, we noted 71% of men were obese and 14.1% had obesity grade III, using a testosterone cut-off of 12.1 nmol/l [23▪▪]. Testosterone levels are reduced with increased waist circumference and obesity [17,24] and approximately 40% of obese nondiabetic men and 50% of obese diabetic men aged above 45 years have low free testosterone [18,25]. The concomitant presence of obesity and diabetes is associated with an additional increase in prevalence of testosterone deficiency approaching 34% [18,19,25,26].

Testosterone therapy in men with testosterone deficiency (hypogonadism) has profound effects on body composition, resulting in reduced fat mass, increased lean body mass (LBM) (Table 1) [27,43,44,45▪,46▪▪,47–53] and significant reduction in anthropometric parameters, such as weight, waist circumference and BMI [20,23▪▪,27,37,39,42,43,48,54–56,57▪,58▪▪–61▪▪,62▪,63▪,64–66] (Table 2). The effects of testosterone therapy on increased LBM and reduced fat mass and the changes in anthropometric parameters were consistently reported in most studies [20–22,23▪▪,24–44,45▪,46▪▪,47–56,57▪,58▪▪–61▪▪,62▪,63▪,64–66], irrespective of testosterone formulations used or duration of testosterone treatment (Tables 1 and 2). On the basis of the consistent findings of testosterone therapy, which demonstrated significant reductions in total body fat mass and increases in LBM [23▪▪,27–44,45▪,46▪▪,47–56,57▪,58▪▪–61▪▪,62▪,63▪,64–66] as well as improvement in weight loss and reductions in waist circumference and BMI (Tables 1 and 2), Allan and Mclachlan [68] proposed the use of testosterone therapy in men with testosterone deficiency for management of obesity. Saad *et al.* [69] further proposed testosterone therapy as a new potential intervention strategy for managing obesity in hypogonadal men (testosterone deficiency). The data from recent studies with long-term testosterone therapy in men with testosterone deficiency, using testosterone formulations which result in sufficient circulating physiological testosterone levels and good patient adherence, reported significant and sustained weight loss, reduced BMI

Table 1. Testosterone therapy increases lean body mass and reduces total body fat mass in men with testosterone deficiency

Study	Testosterone formulation	Treatment period	Lean body mass	Fat mass
Marin *et al.* [27]	Gel	9 months	↑	↓
Snyder *et al.* [28]	Patch	36 months	↑	↓
Kenny *et al.* [29]	Patch	12 months	↑	↓
Crawford *et al.* [30]	Mixed esters	12 months	↑	↓
Ferrando *et al.* [31]	TE	6 months	↑	↓
Steidle *et al.* [32]	Gel	3 months	↑	↓
Wittert *et al.* [33]	Oral TU	12 months	↑	↓
Casaburi *et al.* [34]	TE	3 months	↑	↓
Page *et al.* [35]	TE	36 months	↑	↓
Kapoor *et al.* [20]	Mixed esters	3 months	↑	↓
Bhasin *et al.* [36]	TE	5 months	↑	↓
Kapoor *et al.* [37]	Mixed esters	3 months	↑	↓
Bhasin *et al.* [38]	Gel	6 months	↑	↓
Svartberg *et al.* [39]	Injectable TU	12 months	↑	↓
Allan *et al.* [40]	Patch	12 months	↑	↓
Srinivas-Shankar *et al.* [41]	Gel	6 months	↑	↓
Aversa *et al.* [42]	Injectable TU	24 months	↑	↓
Aversa *et al.* [43]	Injectable TU	12 months	↑	↓
Behre *et al.* [44]	Gel	6 months	↑	↓
Finkelstein *et al.* [45▪]	Gel	4 months	↑	↓
Francomano *et al.* [46▪▪]	Injectable TU	60 months	↑	↓
Bouloux *et al.* [47]	Oral TU	12 months	↑	↓
Pexman-Fieth *et al.* [48]	Gel	6 months	↑	↓
Juang *et al.* [49]	Gel	3 months	↑	↓
Rodriguez-Tolra *et al.* [50]	Gel/Injectable TU	24 months	↑	↓
Frederiksen *et al.* [51]	Gel	6 months	↑	↓
Emmelot-Vonk *et al.* [52]	Oral TU	6 months	↑	↓
Borst *et al.* [53]	TE	12 months	↑	↓

TE, testosterone enanthate; TU, testosterone undecanoate.

and waist circumference [46▪▪,58▪▪–61▪▪,70]. These findings were corroborated by studies in which testosterone therapy produced significant and sustained weight loss [54–56,57▪,58▪▪–61▪▪,62▪,63▪, 64–67] (Table 2).

EFFECTS OF TESTOSTERONE THERAPY ON OBESE MEN WITH TESTOSTERONE DEFICIENCY AND VARIOUS GRADES OF OBESITY

Obesity is categorized into three grades on the basis of patients' BMI. BMI ranging from 30 to 34.9 kg/m^2 falls in grade I, whereas BMI ranging from 35 to 39.9 kg/m^2 falls in grade II and BMI more than 40 kg/m^2 is categorized as grade III. Data reported from three registries [23▪▪,59▪▪–61▪▪], in which long-term testosterone therapy was evaluated in men with testosterone deficiency and varying grades of obesity, suggested that testosterone therapy is effective in producing weight loss in all three grades of obesity. As shown in Fig. 1, long-term testosterone therapy produced significant progressive, sustained weight loss without recidivism in men with testosterone deficiency with various grades of obesity, [23▪▪,59▪▪–61▪▪]. This reduction in weight was also associated with marked and significant reduction in waist circumference (Fig. 2) [23▪▪,59▪▪–61▪▪]. These findings are consistent with those reported in Table 2 and strongly support the concept that testosterone therapy in men with testosterone deficiency represents a novel and useful therapeutic strategy for treatment and management of obesity in hypogonadal obese men.

TESTOSTERONE THERAPY IN MEN WITH TESTOSTERONE DEFICIENCY IS ASSOCIATED WITH WEIGHT LOSS

Testosterone therapy is associated with weight loss [23▪▪,42,56,58▪▪,59▪▪] and obesity is associated with reduced testosterone levels [68,73–77,78▪,79]. The

Table 2. Effects of testosterone therapy on weight loss, waist circumference and BMI

Study	Testosterone formulation	Treatment period	Weight loss	Waist circumference	Body mass index
Marin *et al.* [27]	Gel	9 months	ND	↓	ND
Kapoor *et al.* [20,37]	Mixed esters	3 months	ND	↓	ND
Svartberg *et al.* [39]	Injectable TU	12 months	ND	↓	ND
Heufelder *et al.* [54]	Gel	12 months	ND	↓	ND
Aversa *et al.* [42]	Injectable TU	24 months	ND	↓	ND
Aversa *et al.* [43]	Injectable TU	12 months	ND	↓	ND
Kalinchenko *et al.* [55]	Injectable TU	7 months	↓	↓	↓
Aversa *et al.* [56]	Injectable TU	36 months	ND	↓	ND
Zitzmann *et al.* [57▪]	Injectable TU	9–12 months	ND	↓	ND
Francomano *et al.* [46▪▪]	Injectable TU	60 months	↓	↓	↓
Francomano *et al.* [58▪▪]	Injectable TU	12 months	↓	↓	↓
Haider *et al.* [59▪▪]	Injectable TU	12–72 months	↓	↓	↓
Haider *et al.* [60▪▪]	Injectable TU	12–72 months	↓	↓	↓
Saad *et al.* [23▪▪]	Injectable TU	12–60 months	↓	↓	↓
Yassin and Doros [61▪▪]	Injectable TU	12–60 months	↓	↓	↓
Pexman-Fieth *et al.* [48]	Gel	6 months	↓	↓	↓
Hackett *et al.* [62▪,63▪]	Injectable TU	7 and 20 months	↓	↓	↓
Bhattacharya *et al.* [64,65]	Gel	12 months	ND	↓	ND
Garcia *et al.* [66]	Injectable TU	24 months	ND	↓	ND
Zitzmann *et al.* [72]	Injectable TU	12–192 months	↓	↓	↓

ND, no data; TU, testosterone undecanoate.

potential mechanisms involved in low testosterone levels in obesity encompass complex mechanisms, including increased levels of sex hormone binding globulin (SHBG), low or inappropriate normal levels of luteinizing hormone, adipocyte dysfunction, androgen resistance and insulin resistance. Loss of androgen receptor function increases the number of adipocytes and the accumulation of visceral fat [80]. Low baseline testosterone predicts obesity in men [81] and normalization of physiological testosterone levels reduces the activity of lipoprotein lipase and tryglycerides [77]. Testosterone treatment results in improved insulin sensitivity, lipid oxidation and reduction in fat mass with concomitant gain in fat free mass. Camacho *et al.* [78▪] reported that weight loss is associated with increased testosterone levels, a finding supported by Corona *et al.* [79]. Intervention measures, such as diet and exercise or surgical treatment of obesity, results in increased testosterone levels [79,82,83].

Effects of testosterone therapy on myogenesis and adipogenesis

Androgens regulate myogenesis and inhibit adipogenesis [67,84–88]. Maneschi *et al.* [89] reported that testosterone therapy preserves visceral adipose tissue function, and testosterone deficiency results in derangement and dysfunction of visceral adipose tissue metabolism. Men with testosterone deficiency and obesity have reduced testosterone levels and weight loss produces increased total testosterone levels [79,78▪].

Effects of testosterone therapy on carbohydrate, protein and fat metabolism

Testosterone regulates carbohydrates, proteins and fat metabolism [79,89] and testosterone therapy in men with testosterone deficiency results in normalization of glucose utilization and increased lipid oxidation [90]. Testosterone deficiency affects energy production and utilization and therefore upsets this physiological balance resulting in storage of lipids and increased adipogenesis and altering mitochondrial function [89–94]. Obesity contributes to premature cardiac aging via disrupted mitochondrial biogenesis and function and is an independent risk factor for development of heart failure [92–94]. Testosterone therapy ameliorates this dysfunction.

Effects of testosterone therapy in men with testosterone deficiency on fatigue, motivation, vigor and physical activity

Yu and Traish [95] suggested that testosterone deficiency contributes to fatigue via alterations of mitochondrial function and energy production and

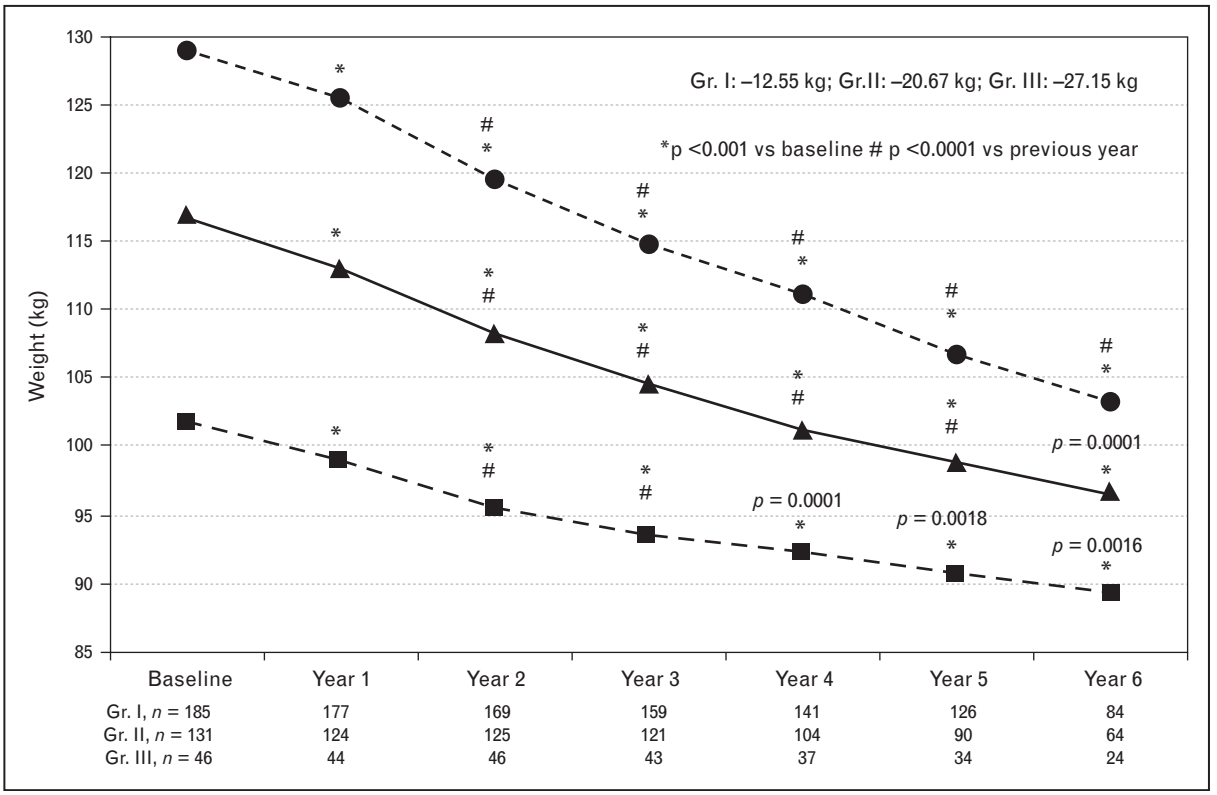

FIGURE 1. Testosterone therapy in men with testosterone deficiency and differing grade of obesity produces significant and sustained weight loss. Hypogonadal men ($n = 362$) with obesity grade I (Gr. I, $n = 185$, mean age: 58.39 ± 8.04 years), grade II (Gr. II, $n = 131$, mean age: 60.62 ± 5.56 years) and grade III (Gr. III, $n = 46$, mean age: 60.28 ± 5.39 years) treated with testosterone undecanoate injections for up to 6 years. Weight expressed in kilogram. Adapted with permission from [60▪▪].

utilization. Testosterone treatment of 1053 hypogonadal men produced increased quality of life with reduced fatigue, increased libido and erectile function and reduced waist circumference [48]. These findings are supported by several other studies in which testosterone therapy resulted in improved motivation, vigor, energy, and reduces fatigue concomitant with significant reduction in waist circumference and improvement in quality of life [44,47,48,57▪,95]. Healthy volunteers, who received a single injection of testosterone undecanoate experienced reduction in fatigue-inertia significantly versus placebo [96]. The increased motivation, energy and reduced fatigue in response to testosterone therapy significantly contribute to more physical activity, thus resulting in increased energy utilization associated with increased muscle mass and improved mitochondrial function. This, in part, explains the observed weight loss with testosterone therapy in men treated for long durations with appropriate testosterone formulations producing physiological levels [58▪▪–61▪▪,72]. In contrast, androgen deprivation therapy (ADT) used in management of hormone-dependent prostate cancer results in fatigue and reduces energy and motivation [95,97].

Effects of testosterone therapy on fat deposition and vascular health

Weight gain is attributed to 88% increased fat mass, and weight loss is associated with 72% decrease in fat mass and 28% decrease in LBM [98]. One of the key observations in testosterone therapy is that testosterone increases LBM, thus increasing resting energy expenditure. Testosterone therapy in men with testosterone deficiency with or without diet and physical activity not only produced reduction in fat mass but also improvements in cardiometabolic function and reduced carotid intima media thickness (CIMT), epicardial fat and trunk fat [46▪▪,58▪▪,70]. Also reduction in CIMT was noted with testosterone but not with diet and physical exercise alone. Reduction in CIMT with testosterone therapy was previously demonstrated [42,71]. Testosterone therapy for 18 weeks reduced ectopic and liver fat in obese men [99▪], suggesting that testosterone therapy has a protective effect on the

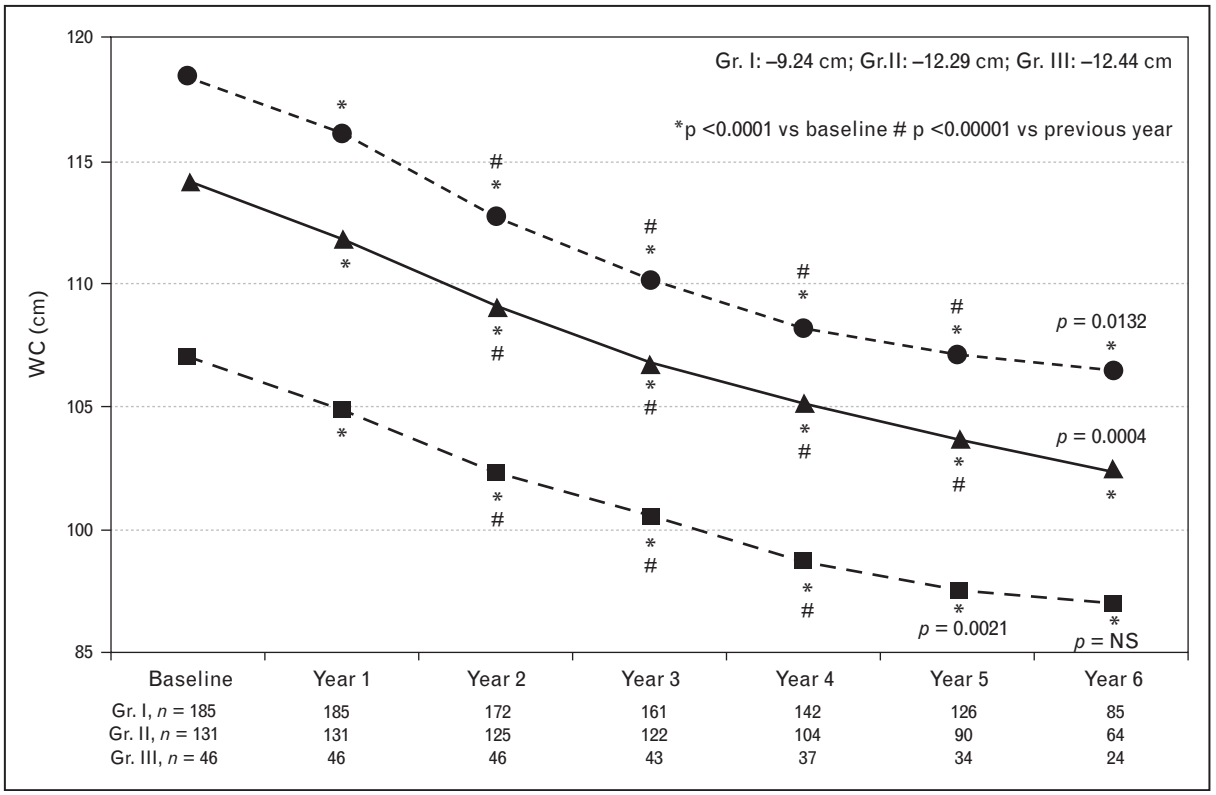

FIGURE 2. Testosterone therapy in men with testosterone deficiency and differing grade of obesity produces marked and sustained reductions in waist circumference. Waist circumference (cm) in 362 hypogonadal men with obesity grade I (Gr. I, $n = 185$, mean age: 58.39 ± 8.04 years), grade II (Gr. II, $n = 131$, mean age: 60.62 ± 5.56 years) and grade III (Gr. III, $n = 46$, mean age: 60.28 ± 5.39 years) Treated with testosterone undecanoate injections for up to 6 years. Adapted from [60▪▪].

cardiovascular system and reduces the risk of CVD. Testosterone therapy for 12 months in men with testosterone deficiency and spinal cord injury significantly improved LBM and resting energy and percentage basal energy expenditure [100]. The predictors of weight regain are reduced levels of testosterone, retinol binding protein 4, SHBG and MetS [101,102▪]. These findings support a role for testosterone therapy in management of obesity.

TESTOSTERONE THERAPY AMELIORATES METABOLIC SYNDROME COMPONENTS, IMPROVES SEXUAL FUNCTION, ENERGY, MOOD, MOTIVATION AND QUALITY OF LIFE

Testosterone therapy ameliorated components of MetS [62▪,63▪,64,65,103▪▪,104]. Testosterone therapy significantly improved Homeostasis Model Assessment (HOMA)-insulin resistance, CIMT and hsCRP, TNF-α, weight, BMI and waist circumference [39,42,43,46▪▪,55,58▪▪,70]. A controlled 5-year study in men with MetS showed significant decreases in weight, waist circumference, BMI, HbA1c, HOMA-insulin resistance, total cholesterol, low density lipoprotein (LDL)-cholesterol, triglycerides, hsCRP, systolic and diastolic blood pressure, and an increase in HDL [46▪▪,70]. Long-term testosterone therapy in men with testosterone deficiency produced a significant reduction in total cholesterol, LDL cholesterol, triglycerides, and increased HDL. Testosterone treatment reduced fasting glucose, HbA1c, the nonspecific inflammatory marker hsCRP and liver enzymes aspartate aminotransferase and alanine aminotransferase suggesting improvement in hyperglycemia and a reduction in the inflammatory response [23▪▪,46▪▪,58▪▪–61▪▪,70,89,105–107]. Further, testosterone therapy reduces inflammation, improves erectile function and increases vigor and reduces fatigue. These changes in physical and behavioral activity result in improved quality of life.

CHALLENGES AND LIMITATIONS OF TESTOSTERONE THERAPY IN OBESE MEN WITH TESTOSTERONE DEFICIENCY

Among the challenges of testosterone therapy is the myth that testosterone causes prostate cancer (PCa). Although this myth has been debunked [108,109], the fear of physicians from litigation has presented a

huge challenge to testosterone therapy in men with testosterone deficiency [110,111]. Recently, another challenge was raised suggesting that testosterone therapy causes myocardial infarctions (MIs), stroke and death [112–114]. Although these reports suffer from serious methodological flaws and poor scientific evidence-based medicine, the purported information that testosterone therapy is harmful has confounded the knowledge gained from more than 4 decades of experience with testosterone therapy, and is in direct contradiction with this large body of actual patient data [115]. A large number of studies have shown that testosterone therapy does not increase the risk of MI, stroke or death [115]. On the contrary, testosterone deficiency is considered a risk of CVD [115]. Jespersen *et al.* [116] reported ADT is associated with greater risk for MI and stroke in men with PCa. Keating *et al.* [117] showed that ADT is associated with worsening of diabetes control and increased despite the use of other diabetes medications.

EXPERT OPINION

One may argue that testosterone therapy has been around for more than 75 years and no data have been reported on the effects of testosterone on weight loss, until recently. So, why now and how could this be explained? Several key reasons explain this deficit in the literature. First, most studies reported on testosterone therapy were of very short duration and this does not permit necessary tissue remodeling and changes in LBM and fat mass, which require longer time periods. Second, testosterone formulations used in many prior studies did not provide sustained physiological levels of testosterone and in most cases the circulating testosterone levels were suboptimal, thus resulting in incomplete responses. Third, in addition, poor patients' compliance to testosterone therapy is of paramount importance in the effectiveness of testosterone therapy. These factors explain, in part, the neutral effects of testosterone therapy on weight observed in some studies. Schoenfeld *et al.* [118] showed that adherence rates to testosterone therapy are variable depending on formulations and therefore differing outcomes are expected.

It should be noted that testosterone deficiency is associated with a shift in fuel metabolism from lipid oxidation toward glucose utilization [119] and testosterone therapy [51,120] increased muscle mass and lipid oxidation in aging men. Furthermore, higher endogenous circulating testosterone levels were associated with reduced loss of LBM in elderly men [121] and testosterone therapy in frail men preserves muscle thickness [122]. Thus, it is not surprising that in obese men with testosterone deficiency, long-term testosterone therapy with formulations that achieve physiological levels, along with adequate adherence, produced significant and sustained weight loss, concomitant with reduction in waist circumference and BMI (Table 2, Figs 1 and 2) [23▪▪,27–44,45▪,46▪▪,47–56,57▪,58▪▪–61▪▪, 62▪,63▪,64–66,72]. Further, long-term testosterone therapy in men with testosterone deficiency produced improvements in cardio-metabolic function, ameliorated MetS components, reduced fatigue, increased vigor and energy and improved quality of life [62▪,63▪,64–66,103▪▪,104–107,123]. We suggest that testosterone therapy offers well tolerated and effective treatment of obesity in men with testosterone deficiency and this novel approach provides a unique opportunity to manage obese men. Other therapeutic targets for the treatment of obesity have been proposed including hypothalamic malonyl-CoA and CPT1c [124,125] and GLP-1, oxyntomodulin, peptide YY, gastric inhibitory peptide and ghrelin [126]. These targets may prove useful in addition to testosterone therapy.

CONCLUSION

Lifestyle modifications are considered a cornerstone in combating obesity. However, this is difficult to maintain over the long term, and the ability to achieve modest weight loss with lifestyle modification is limited, at best. Pharmacotherapy coupled with lifestyle modification provides an alternative to combating obesity with lifestyle changes alone. We propose that testosterone therapy in obese men with testosterone deficiency offers a well tolerated and effective therapy and produces sustained and significant weight loss. Testosterone therapy increases LBM, reduces fat mass and produces sustained and significant weight loss, reduction in waist circumference and BMI. We believe that testosterone therapy in obese men with testosterone deficiency is a unique and effective therapeutic approach to management of obesity. The fact that this therapy has been used over the past 7 decades to treat hypogonadism (testosterone deficiency) and is proven to be well tolerated and effective should be an added tool to the armament for the war on obesity.

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Conflicts of interest

There are no conflicts of interest.

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- ■■ of outstanding interest

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