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REVIEW

Management of male obesity-related secondary hypogonadism: A clinical update

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Abstract

The global obesity pandemic has resulted in a rise in the prevalence of male obesity-related secondary hypogonadism (MOSH) with emerging evidence on the role of testosterone therapy. We aim to provide an updated and practical approach towards its management. We did a comprehensive literature search across MEDLINE (*via* PubMed), Scopus, and Google Scholar databases using the keywords "MOSH" OR "Obesity-related hypogonadism" OR "Testosterone replacement therapy" OR "Selective estrogen receptor modulator" OR "SERM" OR "Guidelines on male hypogonadism" as well as a manual search of references within the articles. A narrative review based on available evidence, recommendations and their practical implications was done. Although weight loss is the ideal therapeutic strategy for patients with MOSH, achievement of significant weight reduction is usually difficult with lifestyle changes alone in real-world practice. Therefore, androgen administration is often necessary in the management of hypogonadism in patients with MOSH which also improves many other co-

morbidities related to obesity. However, there is conflicting evidence for the appropriate use of testosterone replacement therapy (TRT), and it can also be associated with complications. This evidence-based review updates the available evidence including the very recently published results of the TRAVERSE trial and provides comprehensive clinical practice pearls for the management of patients with MOSH. Before starting testosterone replacement in functional hypogonadism of obesity, it would be desirable to initiate lifestyle modification to ensure weight reduction. TRT should be coupled with the management of other comorbidities related to obesity in MOSH patients. Balancing the risks and benefits of TRT should be considered in every patient before and during long-term management.

Key Words: Male obesity-related secondary hypogonadism; Androgen therapy; Testosterone replacement therapy; Obesity; Cardiovascular benefits

Core Tip: The obesity pandemic has increased the prevalence of obesity-related health morbidities including male obesity-related secondary hypogonadism (MOSH). Although weight loss is the ideal therapeutic option for MOSH, testosterone replacement therapy (TRT) is often necessary because of the difficulty in achieving significant weight loss through lifestyle interventions or pharmacotherapy which might also improve obesity-related comorbidities. TRT should be coupled with the management of other comorbidities related to obesity in MOSH patients to optimize management which is updated in this evidence-based review.

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INTRODUCTION

Obesity is a chronic progressive or relapsing disease that left untreated results in increased morbidity and mortality[1]. According to the World Obesity Atlas, 38% of the global population (2.6 billion individuals) were either overweight or obese [body mass index (BMI) ≥ 25 kg/m²] in the year 2020, and this is predicted to reach 51% (4 billion) by 2035[2]. Similarly, 14% of the global population had obesity (BMI ≥ 30 kg/m²) in 2020, and this is predicted to touch 24% by 2035. The prevalence of obesity is higher in women than men[3]. In 2020, 18% of all women and 14% of all men globally had obesity and this is expected to reach 27% and 23%, respectively in the year 2035[3]. Obesity is associated with various metabolic and nonmetabolic complications affecting every organ system in the body. Some obese individuals (especially women) may present with Metabolically Healthy Obesity, characterized by excess subcutaneous fat, relatively lower visceral/hepatic fat, normal insulin sensitivity and inflammatory markers, maintained adipose tissue function and preserved cardiorespiratory fitness[4]. In contrast, some other obese subjects (especially men) present with Metabolically Unhealthy Obesity characterized by visceral adiposity, adipose tissue dysfunction, chronic low-grade inflammation, and higher cardiovascular risk. Obese women often tend to have higher rates of depression and they present early with weight-related issues[5].

Another interesting issue in obese men is obesity-related hypogonadotropic hypogonadism, also known by the term male obesity-related secondary hypogonadism (MOSH)[6]. Recent evidence shows that a similar condition known as female obesity-related secondary hypogonadism, which is distinct from polycystic ovary syndrome, may also be present in women[7]. It is important to update the pathobiology and management algorithms for MOSH to inform evidence-based clinical practice decisions, especially when we consider androgen replacement therapy. This review is an attempt with the back-up of the most up-to-date review of current global scientific literature.

PATHOPHYSIOLOGY OF MOSH

There is a complex interplay of various feedback mechanisms with neural and hormonal signaling molecules contributing to MOSH[6]. Obesity with expanded visceral adipose tissue leads to secondary hypogonadism with an 8.7-fold higher risk in patients with a BMI > 30 kg/m². Testosterone (T), even in suboptimal levels, facilitates the differentiation of pluripotent stem cells into adipocytes to increase the aromatization of T into estradiol and to cause a negative feedback mechanism at the hypothalamus and pituitary levels that in turn suppresses the gonadal stimulation and T release. The arcuate nucleus and periventricular nucleus of the hypothalamus release neuropeptide Kisspeptin, which in turn stimulates the release of gonadotrophin-releasing hormone (GnRH)[6].

This link was named the Cohen hypothesis based on the finding that T and obesity have a bidirectional relationship in which obesity acts as a strong independent risk factor for T deficiency and suboptimal T levels can exacerbate obesity[6]. The hypogonadal-obesity-adipocytokine hypothesis is an extension of Cohen's theory, wherein T enhances the activity of lipoprotein lipase enzyme, leading to a rise in triglyceride (TG) uptake into adipocytes. With larger numbers of adipocytes, there is an increase in insulin resistance, production of pro-inflammatory cytokines including tumor necrosis factor-α, interleukin (IL)-1 and IL-6 and increase in leptin and estradiol levels. Leptin, produced by adipocytes, stimulates hypothalamic neurons to release GnRH, and subsequently, luteinizing hormone (LH) from the pituitary gland, and potentiates the release of T. Leptin can directly and indirectly, *via* receptors in testicular tissue, inhibit gonadotrophic actions on Leydig cells to worsen T deficiency. These neurons become resistant to the actions of leptin in obesity. A sustained state of hypogonadotropic hypogonadism is contributed by a reduction in GnRH signals, inhibiting the neuronal release of Kisspeptin and excess estradiol. In circulation, approximately 98% of T is bound to albumin and sex hormone-binding globulin (SHBG). Suboptimal levels of SHBG and T significantly contribute to insulin resistance and a pre-diabetic state. Hyperinsulinemia due to reduced insulin sensitivity in peripheral tissues contributes to central hypogonadism through the modulation of GnRH and gonadotrophin output and secondly to peripheral hypogonadism through direct actions on Leydig cells[6]. A schematic representation of the pathogenesis of MOSH is shown in Figure 1.

Another hypothesis, the Gut Endotoxin Leading to a Decline IN Gonadal function (GELDING) theory, states the role of metabolic endotoxemia[8]. This is the acronym for GELDING. Gut microbiota with an average of 1.5 kg (100 trillion) of bacteria residing in the human bowel produce various proinflammatory cytokines. High-calorie and fat-based diets contribute to the release of bacterial endotoxins from the gut. Exposure to these lipopolysaccharides causes impaired testicular function, thereby contributing to T deficiency.

Adipose tissue plays a major role in glucose homoeostasis and insulin sensitivity. The inverse correlation between visceral fat and testosterone levels is strong[9]. Testosterone increases lipolysis by increasing the number of β-adrenergic receptors. The action of testosterone on subcutaneous and visceral adipose function is different. Subcutaneous fat accumulation in the truncal area is highly predictive of low plasma concentrations of free testosterone rather than visceral adiposity[9]. There are no mechanistic studies that address the differential response to testosterone in different adipose tissues. The hypogonadal-obesity-adipocytokine hypothesis takes into consideration high aromatase activity in adipocytes converting testosterone to oestradiol[6]. TG storage in adipocytes is increased by reduced testosterone by stimulating pluripotent stem cells to mature into adipocytes[9].

DIAGNOSIS OF MOSH

Definition

Though definitions vary, a diagnosis of MOSH is usually made in obese men with BMI of ≥ 30 kg/m^2 with clinical features of hypogonadism (including impaired sexual, physical or mental performance, impaired sexual characteristics, gynaecomastia, breast pain, sleep problems, dysglycemia, flushing, low bone mineral density (BMD) or unexplained anaemia), biochemical evidence of hypogonadism with low total, free or bioavailable testosterone along with low or inappropriately normal LH, with other causes of hypogonadism including hyperprolactinemia having been excluded systematically[10].

Biochemical testing

For the diagnosis of MOSH, a cut-off level of total testosterone (TT) ≤ 12 nmol/L (346 ng/dL) in men with clinical manifestations of hypogonadism is used[11]. Since hyperinsulinemia, type 2 diabetes mellitus (T2DM) and metabolic syndrome (MetS) are associated with reduced SHBG concentrations, in the context of MOSH, it is recommended that free testosterone (free T) levels be calculated in order to avoid unnecessary testosterone replacement therapy (TRT). Free T can be determined by multiple methods like physical separation from the protein-bound forms by equilibrium dialysis or ultracentrifugation. Although equilibrium dialysis is the most accurate method among these, it is expensive, time-consuming and practically unfeasible[12]. SHBG and albumin level-based calculations have also been used to estimate free T. For example, the Vermeulen method, though accurate, can slightly overestimate free T. In cases of MOSH, SHBG should be measured during diagnostic workup to calculate free testosterone. According to the European Male Ageing Study (EMAS) study and a longitudinal evaluation of the same study, reduced free T (< 220 pmol/L) is better than total T alone in the detection of MOSH, especially for thresholds between 8.0 and 11.0 nmol per litre[13]. Diurnal variation gets significantly blunted in men > 40 years. However, it is recommended that testosterone be measured in the morning for all age groups. Measurement of testosterone levels should preferably be done while fasting, using a validated technique and not during an acute illness. Low testosterone should be confirmed on two occasions, preferably four weeks apart[6].

In the presence of reduced T concentrations, an LH concentration ≥ 9.4 IU/L is used to define primary hypogonadism, whereas low or low-normal LH concentrations define secondary hypogonadism[14]. MOSH is mostly characterized by a secondary or mixed, rather than primary hypogonadism. While the recent clinical practice guidelines by the Italian Society of Andrology and Sexual Medicine (SIAMS) and the Italian Society of Endocrinology (SIE) consider a cut-off of 12 nmol/L (346 ng/dL) for TRT, the British Society for sexual medicine guidelines recommend TRT in cases with total T < 8 nmol/L (< 231 ng/dL), or free T < 225 pmol/L (< 0.225 nmol/L). Those with total T between 8-12 nmol/L (231-346 ng/dL) may be given a TRT trial for six months based on symptoms[14].

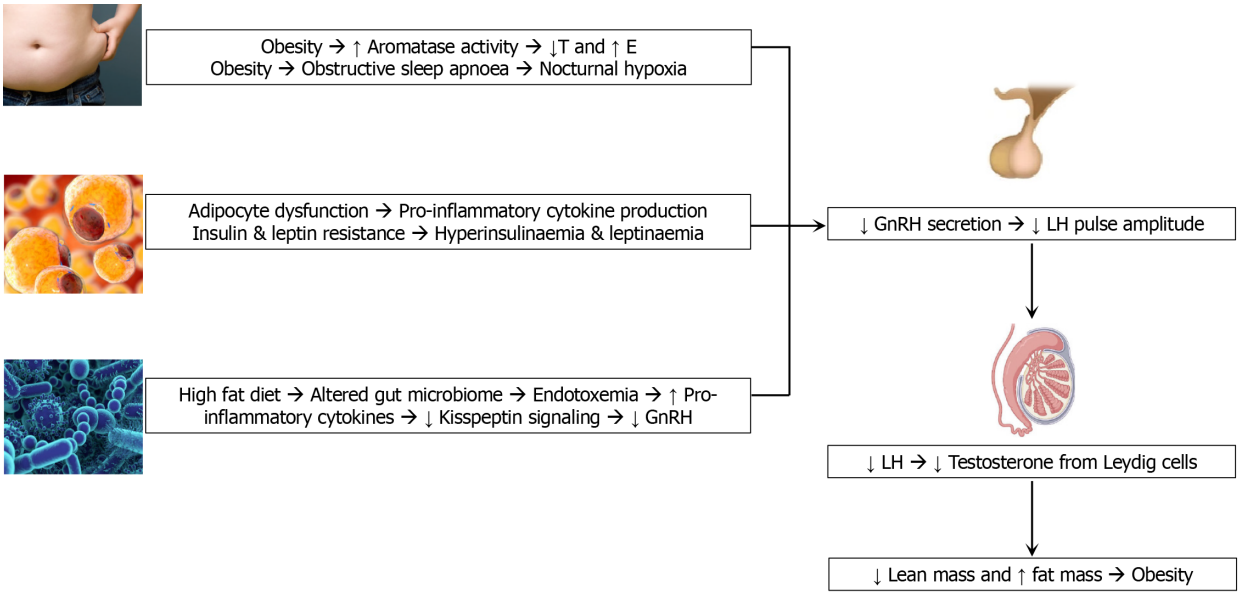

Figure 1 The pathobiology of male obesity-related secondary hypogonadism. E: Estradiol; GnRH: Gonadotropin-releasing hormone; LH: Luteinizing hormone; T: Testosterone.

MANAGEMENT OF MOSH: TO TREAT OBESITY OR HYPOGONADISM OR BOTH?

While obesity and hypogonadism are linked bidirectionally, there is an ongoing debate on whether to focus first on the treatment of obesity which can lead to improvement in gonadal function or to start testosterone replacement to correct hypogonadism first, with expected beneficial effects on body weight and metabolic parameters. In an attempt to address this debate, the following sections focus on the effects of obesity treatment on male hypogonadism and the role of Testosterone therapy on obesity.

Effect of weight loss on hypogonadism

Healthy lifestyle changes can help achieve significant weight loss. Hypothalamic-pituitary-testicular (HPT) axis suppression and testosterone deficiency in MOSH are potentially reversible, without the need for testosterone treatment. A meta-analysis of several studies found that significant weight loss can induce an increase in T levels[15], along with an increase in SHBG, calculated free T, LH , and follicle-stimulating hormone (FSH), and a reduction in estradiol (E2). This has been seen in several observational studies. Low-calorie diet caused a weight loss of 9.8% and therefore induced an average T increase of less than 3 nmol/L, while bariatric surgery, with a weight loss of 32% increased T levels three times higher (almost 9 nmol/L)[16,17].

Interestingly, this is similar to the degree of increase in T levels seen with transdermal T supplementation with a patch or gel in a recent meta-analysis[18]. Thus, consistent weight loss can be as efficient as TRT concerning an increase in T levels. Weight loss intervention, especially, bariatric surgery induces a reduction in estradiol and possibly, the positive effect of these interventions on the HPT axis is the reduction of the estrogen-dependent negative feedback and thereby inhibition of Kiss-1[19].

Lifestyle changes to treat obesity

Functional hypogonadism in MOSH can be managed with lifestyle measures. If lifestyle measures can achieve significant weight loss, it may obviate the need for T treatment. The United States Preventive Services Task Force has recommended effective, intensive, behaviour-based weight loss interventions to help adults with obesity achieve a weight loss of ≥ 5% through changes in diet and physical activity. After one year, an average weight loss of 2-3 kg is observed with such interventions, and can even achieve a weight loss of up to 9 kg[20]. A loss of 5%-10% of initial body weight is a target as well as a measure of successful weight loss as per the European Practical and Patient-Centred Guidelines (2019) for adult obesity management in primary care[21]. In a recent trial, there was a reduction in body weight (compared to baseline) by approximately 4 kg (4%), 7 kg (7%), and 5 kg (5%) within 10 wk, six months, and one year, respectively in the intervention group and good adherence to dietary recommendations even at one year. There were significant reductions in body weight, BMI, waist circumference (WC), remnant cholesterol, and resting heart rate at 10 wk, and these changes were maintained for one year[22]. The dietary interventions, with or without exercise are likely to improve the gonadal function with improvement of T levels[23]. In a study of 68 men who attained a mean loss of 10.3-10.8 kg ± 1.2 kg over the 52-wk study period, there was a significant increase in TT and FT[24].

In the EMAS study, it was shown that around a 20% reduction in BMI is required to produce a significant increase in FT level[25]. Ketogenic diets (KD) can improve the metabolic and weight patterns in obese patients. However, the effect on testosterone levels is less well understood. In a recent meta-analysis comprising eight trials and 230 patients, five trials enrolled subjects on normocaloric KD and three trials enrolled subjects on very low-caloric KD (VLCKD). TT increased in

111 patients, more with VLCKD compared to normocaloric KD. Meta-regression analyses showed significant correlations between the post-KD testosterone rise with patients' age and weight loss[26].

PHARMACOLOGICAL MANAGEMENT OF OBESITY

Obesity is a chronic disease associated with a chronic low-grade inflammatory state and immune dysfunction. Significant improvement in metabolic processes as well as decrease in overall mortality has been reported in several studies with multiple modes of treatment. Glucose-lowering medications have been employed in prediabetic and diabetic individuals. Improvements in erectile dysfunction after anti-diabetic drug therapy may be ascribed to indirect mechanisms such as the reduction of hyperglycaemia, excess body weight, high blood pressure, and the amelioration of other detrimental factors. However, a direct effect of glucose-lowering agents on both endothelial and smooth muscle cells is reasonable.

Metformin

This drug has evidence for anti-obesity, renal, cardioprotective and anticancer roles. There is an anti-androgenic effect as well as a negative impact on testicular and reproductive health[27]. Prolonged duration of metformin-based therapy reduces T levels and counteracts the T elevation accompanied by improved blood glucose[28]. Low T levels have also been observed in patients on metformin, regardless of age, duration of the disease and hemoglobin (HbA1c)[29]. A recent study indicated that for fathers who took one or more prescriptions for metformin during the development of fertilizing sperm, the likelihood of their male offspring having genital birth defects was increased[30]. Mechanisms underlying the dangerous effects of metformin on human testicular health are unclear.

Pioglitazone

This insulin sensitizer appears to improve venous occlusive function through a mechanism independent of glycaemic control[31].

Sodium-glucose cotransporter-2 inhibitors

Regarding gliflozins, animal studies showed that empagliflozin improves erectile function in diabetic rats by increasing NO-mediated relaxation of erectile tissue[32]. Dapagliflozin may protect against diabetes-induced spermatogenic dysfunction *via* GLP-1R/PI3K/Akt-dependent pathway. Treatment with dapagliflozin increases T secretion in obese patients with uncontrolled T2DM and hypogonadism by the extent of weight loss and reduction in testis inflammation. An open-labelled non-randomized pilot study amongst thirty Caucasian patients demonstrated that treatment with dapagliflozin plus tadalafil resulted in improvement in erectile dysfunction, suggesting the ability of dapagliflozin to enhance the efficacy of tadalafil[33].

Glucagon-like peptide-1 receptor analogues

Glucagon-like peptide-1 receptor analogues-based therapy may potentially act on the HPG axis, fostering LH secretion by hypothalamic-pituitary neurons, T production by the testis, ameliorating the semen quality and improving erectile function. Supplementation of liraglutide to metformin therapy ameliorated endothelial functions of the corpus cavernosum of male obese subjects with T2DM, resulting in the recovery of erectile performance[34]. In the Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND) trial, long-term treatment with dulaglutide was also found to reduce the incidence of moderate or severe erectile dysfunction in middle-aged men with T2DM[35]. In a prospective randomized open-label study, the treatment of obese men with liraglutide induced a significant increase in serum TT levels (2.6 nmol/L ± 3.5 nmol/L), improvement of LH and FSH secretion along with an average weight loss of 7.9 kg ± 3.8 kg compared with a 0.9 kg ± 4.5 kg loss only with TRT[36]. Similar encouraging results are expected with other GLP-1 agonists.

BARIATRIC SURGERY

Metabolic and bariatric surgery (MBS) has evolved over the past three decades as a therapeutic strategy for obesity. MBS can reverse obesity-induced hypogonadism in a certain subset of individuals. TRT could be additionally employed if these measures fail to relieve symptoms and normalise testosterone levels. Recent guidelines on MBS and its indications by the American Society for Metabolic and Bariatric Surgery (ASMBS) and the International Federation for the Surgery of Obesity and Metabolic Disorders focused on the currently available surgical treatments for severe obesity and the criteria for selection, efficacy, and risks of surgical treatments for severe obesity and nonsurgical programmes that could be the initial therapy for severe obesity[37].

A BMI of 40 kg/m^2, or 35 kg/m^2 with co-morbidities, is a threshold for surgery that is applied universally. Currently, the dominant procedures are sleeve gastrectomy and Roux-en-Y gastric bypass, and together these procedures account for approximately 90% of all operations performed worldwide. Other procedures are adjustable gastric banding, biliopancreatic diversion with a duodenal switch and one-anastomosis gastric bypass.

A recent clinical study from Spain by Miñambres *et al*[38] revealed that weight loss attained after bariatric surgery among 12 subjects (five Sleeve gastrectomies and seven Gastric Bypass), increases TT, free testosterone and SHBG, resulting in the complete resolution of MOSH in men with severe obesity. The results demonstrate improved sexual

function without an impact on sperm concentration and motility and an overall decline of morphology over time. In another study by Rigon *et al*[39], among 29 men undergoing bariatric surgery with a mean baseline weight of 155.26 kg ± 25.88 kg, there were significant improvements in TT levels from 229.53 ng/dL ± 96.45 ng/dL to 388.38 ng/dL ± 160.91 ng/dL ($P < 0.001$).

A recent systematic review involving 14 studies and 508 patients clearly showed remarkable benefits of improvement of T levels and erectile function in patients following weight loss after bariatric surgery[40]. Trials evaluating the effect of MBS on semen morphology are highly variable and inconsistent, with small prospective studies reporting a decrease in the percentage of sperm with normal morphology. However, a recent meta-analysis described that bariatric surgery had been associated with improved sperm morphology 12 months post-surgery[41].

OTHER THERAPEUTIC OPTIONS

Gonadotrophins such as human chorionic gonadotropin (hCG) or FSH are effective in increasing testosterone levels and semen parameters but are costly and require administration *via* injection. They currently require approval, prescription, and follow-up from specialist centres. Pulsatile GnRH is a less attractive option due to both the cost and the impracticality of continuous infusion. Selective oestrogen receptor modulators (SERMs) such as clomiphene citrate have been shown to increase testosterone levels without a negative impact on fertility, though there is a lack of long-term data regarding their impact on hypogonadal symptoms. The aromatase inhibitors (AIs) may also raise testosterone levels but are associated with reduced oestradiol levels and BMD, and their use requires close, long-term monitoring. Further studies of clomiphene and AIs in conjunction with testosterone therapy are required to confirm whether these agents can be used synergistically. This might mitigate the risk of adverse events of TRT in terms of reduced fertility and symptoms associated with increased oestradiol levels.

Weight reduction and MOSH-summary of the evidence: Overall, results suggest that a significant degree of weight loss does lead to improvement in serum T levels in those with hypogonadism. Lifestyle modification and bariatric surgery for those with severe obesity seem to show the best results in this regard. Some of the pharmacotherapeutic agents have shown a few additional benefits concerning erectile dysfunction or semen motility through unknown mechanisms. The choice of agent should be guided by the presence of other comorbidities like diabetes, or contraindications. The detrimental effects of metformin on sperm production or functioning will have to be elucidated in further studies.

ROLE OF TESTOSTERONE IN THE MANAGEMENT OF MOSH

The management of MOSH should be done with a multipronged approach. The relationship between obesity and T is bidirectional. T exerts multiple effects on body composition, lipid parameters, glycemic parameters, and overall cardiometabolic health. TRT is also fraught with possible adverse effects on cardiovascular events. Ensuring adequate weight loss with an increase in T levels is the cornerstone of therapy in MOSH-the effects of TRT remain controversial. The following section focuses on its role in multiple aspects of MOSH.

Effects on body weight

Some observational, registry-based studies had reported weight loss with TRT. However, analysis of controlled studies revealed alterations in body composition while overall body weight was unaltered. Trials of men with late-onset hypogonadism (LOH) have shown a decline in WC and body fat percentage with TRT but without any change in BMI[42]. One study reported a decrease in body weight by 16 kg, BMI by five points and a reduction in WC by nine cm over an observational period of five years[43].

In one of the oldest meta-analyses on this topic by Isidori *et al*[44], the authors did not find any significant effect of TRT on BMI. There were significant changes in body composition though, with up to 1.6 kg decrease in fat mass and a similar increase in lean body mass. Another meta-analysis, including multiple observational studies as well as RCTs on the effects of TRT in the management of hypogonadism, indicated a decrease in BMI, weight and WC by 1 kg/m^2, 6 kg and 7 cm respectively[45]. However, the difference was only seen in uncontrolled studies, among older and more obese subjects, and studies with longer duration of follow-up[46]. The reduction of fat mass was observed in both placebo-controlled (-2.13%) and uncontrolled (-4.56%) studies. When the meta-analysis was done including only observational studies with 4513 patients, TRT was found to be associated with a time-dependent reduction in body weight by 3.5 kg and WC by 6.23 cm over 24 months.

Effects on body composition

In contrast with the effects of TRT on body weight and BMI, which have mostly been seen in observational studies and among older and more obese subjects, the beneficial changes in body composition have been more consistently seen in RCTs as well, with an increase in lean mass and decrease in fat mass. Since there is an inverse association of muscle mass with diabetes mellitus risk, the anabolic effects of T to increase lean mass and reduce fat mass might be a potential mechanism for metabolic risk reduction with T. A study using data from the 1999-2000 NHANES revealed that men in the highest tertile of total T had higher lower-body and upper-body lean mass and lesser upper body fat mass [β = -6.1%; 95% confidence interval (95%CI): -10.1 to -2.1, $P = 0.005$] than those in the lowest quartile, indicating that even at physiologic levels, an association exists between higher levels of T and favourable lean and fat mass distribution[47].

A meta-analysis of TRT in elderly men reported an increase in lean mass weight from 1.65 kg to 6.20 kg (an effect estimate of 3.59), and a decrease in fat mass (an effect estimate of -1.78). However, the authors admitted to having a high level of heterogeneity between the included studies[48]. An RCT on the effects of TRT in obese men on a hypocaloric diet indicated that those on placebo lost both fat and lean mass whereas the weight loss in those on TRT was almost exclusively due to body fat loss[49]. A group of 202 men received goserelin acetate, placebo or testosterone gel along with anastrozole, the latter to suppress the conversion of testosterone to estradiol[50]. The percentage of body fat increased in groups receiving placebo or testosterone daily without anastrozole whereas lean mass and thigh-muscle area decreased in men receiving placebo and in those receiving testosterone without anastrozole. There was wide variability in the amount of testosterone required to maintain lean mass, fat mass and strength.

Effects on muscle strength

The anabolic effects of T on muscle growth and function are well known, so much so that over the past several decades, T remains one of the most common substances abused by athletes to improve muscle mass, muscle recovery and endurance. In the early meta-analysis by Isidori *et al*[44], the effect of TRT on muscle mass was unequivocally documented compared to placebo. In contrast, in a later meta-analysis, focusing on androgen trials in men aged above 65 years, TRT, especially with parenteral T, was found to cause a moderate increase in muscle strength, with larger effects for lower extremity and total body strength measures[51]. More recent trials on elderly community-dwelling elderly males with hypogonadism have revealed TRT to increase muscle strength measures like leg-press strength, chest-press strength and stair-climbing power[52]. While the results are still controversial, increased muscle strength with TRT, especially in elderly, frail individuals, is a notable finding that will lead to a better exercise ability in such individuals. Finkelstein *et al* [50] highlighted that while androgen deficiency accounted for a decrease in muscle size and strength, estrogen deficiency chiefly accounted for an increase in body fat, and a decline of both contributed to the decline in sexual function.

Effects on lipid profile

Most epidemiologic studies have reported an association of low T levels with an atherogenic lipid profile but higher high-density lipoprotein (HDL) cholesterol[53]. Higher T levels are associated with less atherogenic smaller very-low-density lipoprotein (VLDL) particles and lower ApoB to Apo A-1 ratio[53,54]. TRT reduces plasma HDL cholesterol depending on the dose and route of administration[55]. In interventional studies, TRT was reported to be associated with a modest reduction in HDL cholesterol in hypogonadal men. The reduction in HDL cholesterol is predominantly seen with non-aromatisable oral androgens than injectable T esters or transdermal T. Regarding its effects on LDL, few studies have reported a significant reduction in LDL cholesterol. In a study on 161 men with LOH, the total and LDL cholesterol declined significantly, with no significant changes in HDL cholesterol and TG[56]. In a meta-analysis of 59 RCTs, when the authors included only RCTs enrolling hypogonadal subjects with T levels < 12 nmol/L, TRT achieved a reduction of total cholesterol as well as TG levels without any change in HDL cholesterol[57]. Overall, the results of clinical studies on the effects of TRT on lipid parameters are conflicting.

Effects on glycemic parameters

Several epidemiologic studies found an association of low total T levels with increased risk of T2DM, though the association was weak or absent with free T, hinting at SHBG being the primary determinant of the observed correlation[54,58,59]. The mechanisms linking low T and worsening of insulin resistance could be loss of skeletal muscle mass, increased fat mass, and effects of T on lipid oxidation and mitochondrial function[60]. A prospective study suggested that low T is associated with incident T2DM in men[61].

Clinical trials studying the metabolic effects of TRT in men with T2DM and MetS have yielded conflicting results. In their euglycemic clamp-based studies, Dhindsa *et al*[62] found that three weeks of TRT had no effects on insulin sensitivity or other glucose parameters, but 24 wk of TRT led to changes in body composition and improvement in insulin sensitivity. Only a few RCTs studied the effects of TRT on glucose values or insulin sensitivity indices as primary endpoints. One of the largest studies on T2DM or MetS subjects (n = 220), the TIMES-2, did not find a significant reduction in HbA1c or BMI after 26 wk of topical T, although a slight improvement in homeostatic model assessment for insulin resistance (HOMA-IR) was observed[63]. In the largest RCT conducted exclusively in 199 men with T2DM, parenteral T undecanoate (TU) resulted in significant improvement of HbA1c concentrations, particularly in those with poor glycemic control at baseline with HbA1c ≥ 7.5%[64]. Some other studies failed to find any improvement in HbA1c or HOMA-IR despite an improvement in body composition[65]. A few uncontrolled registry-based observational studies suggest improvement in glucometabolic parameters with TU in men with T2DM and MetS and prevent their progression from pre-diabetes to T2DM[66-68]. However, these studies were mostly short-term, and had methodologic limitations. Their results were inconsistent, and the observed improvements were only modest.

In a meta-analysis of RCTs, TRT reduced fasting plasma glucose (FPG) by 0.34 mmol/L and HOMA-IR by 0.8[57]. A review of RCTs on men with T2DM and baseline T between 12 to 15 nmol/L (346-432 ng/dL) showed a reduction in FPG by 1.2 mmol/L over a period of 3 to 12 months[69]. In a more recent meta-analysis of 833 men with baseline T between 6.7 to 10.1 nmol/L (193-291 ng/dL), TRT improved measures of insulin resistance but did not reduce HbA1c%[70].

In the recent testosterone for prevention of DM trial, 1004 men were randomised to TRT to study the efficacy of TRT in the prevention or reversal of newly diagnosed T2DM in men enrolled in a lifestyle programme[71]. At the end of two years, TRT resulted in a greater likelihood of normal oral glucose tolerance test [odd ratio (OR): 1.20, 95%CI: 1.04-1.38, P = 0.012] and lowered FPG (OR: -0.17 mmol/L, 95%CI: -0.29 to -0.06, P = 0.004). TRT reduced the risk of T2DM by 40% in men with high WC having impaired glucose tolerance or newly diagnosed T2DM. The benefits of TRT were similar for men with baseline T < 11 nmol/L (317 ng/dL) or more. The relationship between low T concentration and obesity and

the risk of T2DM is bidirectional in middle-aged and older men. However, the effects of TRT alone in this regard need further research. A holistic approach, incorporating healthy lifestyle behaviours and optimised management of medical risks, seems to be a more prudent and evidence-based approach to metabolic risk mitigation in men before TRT.

In a recently published sub-study of the TRAVERSE trial, the effect of T on progression from prediabetes to diabetes in men with hypogonadism was evaluated; there were no significant differences in the risk of progression to diabetes between the testosterone and placebo groups at any point of time ranging between six to 48 months of follow-up (P = 0.49)[72]. The rates of prediabetes/diabetes remission and also the changes in glucose and HbA1c levels were similar in testosterone- and placebo-treated men. The encouraging data with TRT on diabetes mellitus prevention is limited to studies with up to a two-year observation period, and in subjects with borderline hypogonadism who were also following a concomitant strict, lifestyle programme.

Effects on blood pressure

Serum levels of T are believed to drive the differences in BP between men and women that become apparent post-puberty [73]. Androgen receptor (AR) signaling increases the activity of the renin-angiotensin-aldosterone system and orchiectomy or the use of AR antagonists reduces plasma renin activity as well as salt-induced hypertension in male rats[74]. T also increases the mRNA expression of renal angiotensinogen[75]. T administration could lead to transient sodium and fluid retention during the first few weeks of treatment, and some older men may manifest edema[76]. Despite all these effects of T, men with hypogonadism have higher systolic blood pressure than eugonadal men[63] and TRT has not resulted in increased BP in most studies[76,77]. However, some recent studies with oral TU and with subcutaneous T enanthate detected a small rise in clinic and 24-h ambulatory BP following 120 d to 180 d of treatment, and the effect was mostly seen on systolic than diastolic BP[78,79].

Effects on cardiovascular events and mortality

T has several potentially beneficial effects on the cardiovascular system. In addition to its effects on lipid parameters, BP and glucose intolerance, T has potent vasodilator action by inhibiting L-type calcium channels causing increased coronary blood flow[79,80]. It also can improve endothelial function and reduce vascular reactivity. TRT, by downregulating *SERCA-2a* expression, reduces the calcium accumulation within the sarcoplasmic reticulum, thereby attenuating cardiac inotropy[81]. T has also been shown to retard atherosclerosis in some preclinical studies but not all[67,75].

Cross-sectional and longitudinal epidemiologic studies revealed an inconsistent relationship between T levels and cardiovascular events[68,82,83]. Epidemiologic studies can only suggest association and not prove causality. Reverse causality is also a possibility, indicating that T is a marker of health, and men at high risk of mortality also have low T levels. Interestingly, Ruige *et al*[83], found that high T levels were associated with low risk for CV events in men > 70 years of age but not in younger men. In the Rotterdam study, men with the lowest quartile of T levels had greater progression of carotid intima thickness than men in the highest quartile of T. However, there was no difference in coronary artery calcium scores[84,85].

A meta-analysis by Corona *et al*[69] reported an association of low T levels with high cardiovascular and overall mortality. Another meta-analysis of 11 RCTs also found that lower T levels were associated with a higher risk of all-cause mortality, especially cardiovascular mortality[86]. Whereas TRT can have positive and negative effects on cardiovascular health, CV concerns also need to be factored in, especially when TRT is planned for elderly men with high CV risk. The therapeutic benefits of androgen therapy in MOSH are shown in Figure 2.

Another multi-centre RCT, the TRAVERSE study[87], on 5246 men between 45 to 80 years of age who had hypogonadism and also pre-existing cardiovascular disease or a high risk for the same, was recently published. The participants were randomly assigned to receive daily transdermal 1.62% testosterone gel (dose adjusted to maintain testosterone levels between 350 ng/dL and 750 ng/dL) or placebo gel. The primary cardiovascular endpoint was the first occurrence of any component among a composite of cardiovascular deaths, nonfatal myocardial infarction, or nonfatal stroke. At a mean follow-up of 33.0 months ± 12.1 months, the occurrence of the primary cardiovascular end-point event was non-inferior in the testosterone group compared to the placebo group (7.0% in the testosterone group *vs* 7.3% in the placebo group [hazard ratio (HR): 0.96, 95%CI: 0.78-1.17; P < 0.001 for noninferiority]. The incidence of each of the events of the composite primary cardiovascular endpoint was similar in the two groups. There was a higher incidence of atrial fibrillation, acute kidney injury and pulmonary embolism in the testosterone group.

Effects on sexual function in middle-aged and elderly males

MOSH is particularly prevalent in middle-aged and elderly males. TRT has demonstrated improvement in sexual function in young men with primary or secondary hypogonadism as well as in middle-aged men with mildly or moderately low T levels[88-90]. While the effects on sexual activity in older men were controversial in older studies, the T trials demonstrated modest improvement in sexual interest and activity with TRT in elderly males with documented hypogonadism, with greater effects seen on libido and sexual activity than on erectile function. A recent meta-analysis showed that TRT is most effective when serum T is < 10.4 nmol/L (< 300.0 ng/dL) and not very effective when T > 12.0 nmol/L (> 350.0 ng/dL)[46,91]. Another meta-analysis found that TRT alone can modestly improve mild, but not severe, erectile dysfunction with an improvement by 2-3 points on the international index of erectile function-Erectile function domain (IIEF-EFD, 2-3 points; effect size 0.30). The degree of improvement in sexual activity is higher in those with lower baseline T and steeper improvement in T levels[92].

Recently, the Sexual Function Study, nested within the parent TRAVERSE trial[93] aimed to find the efficacy of TRT in improving sexual activity, hypogonadal symptoms, libido and erectile function among middle-aged and older hypogonadal men reporting low libido with the primary outcome being change in sexual activity score. TRT with 1.62% gel

Figure 2 Therapeutic benefits of androgen replacement therapy in male obesity-related secondary hypogonadism. CV: Cardiovascular; SBP: Systolic blood pressure.

was associated with significant improvement in sexual activity compared to placebo with a mean between-group difference of 0.49 and 0.47 acts per day at 6 and 12 months, respectively, omnibus $P = 0.011$. The beneficial effects of TRT were maintained at 24 months. On analyzing individual secondary outcomes, TRT improved hypogonadal symptoms and sexual desire, but not erectile function.

Beneficial effects of TRT on mental health

TRT is thought to affect mood, energy, and health in multiple ways. Some trials have demonstrated significant improvements in the quality of life (QoL) with TRT when validated questionnaires were used like the Q-LES-Q or SF-36[92,94]. However, there are also trials showing no significant effects of TRT on health-related QoL, and therefore, no definite conclusions can be drawn[95,96]. Basaria *et al*[97] reported negative effects of TRT in hypogonadal males with subthreshold depression, which they propose might have been due to the use of insensitive Howl measures. In one large RCT from Japan, improvement with TRT was seen in the physical subdomain of the SF-36 scale with slight improvement in the emotional subdomain[98]. The effect on the physical subdomain is of particular interest in the context of MOSH, as the increased exercise capacity can translate into improved weight loss.

Concerns with the use of TRT in MOSH

The chief concerns about TRT relate to the pro-stimulatory and pro-differentiating effects of T on prostate and breast cancers. An increased risk for incident prostate cancer, prostate-related adverse events, increase in lower urinary tract symptoms (LUTS) or prostate volume and excess risk in breast cancer are suggested, though not convincingly seen in short-term studies following TRT in men with low T. The Endocrine Society recommendations listed in Table 1 are against the use of TRT in those at very high risk of adverse effects including metastatic prostate cancer or breast cancer, or those at moderate to high risk. However, the CVD risk and fertility concerns related to TRT are discussed in detail, since they are the most relevant in the context of MOSH. Formulation-specific adverse effects and monitoring are tabulated in Table 2.

Adverse effects of TRT on fertility

While TRT is used to induce secondary sexual characteristics and to improve libido and sexual functioning, TRT does not support spermatogenesis due to negative feedback on GnRH and gonadotroph secretion. One study showed that regular TRT in 271 healthy fertile men induced azoospermia after 4 months, and restoration of spermatogenesis after stopping TRT took nearly six months[99]. There have been concerns about persistent suppression of spermatogenesis after discontinuing TRT. TRT is not recommended for hypogonadal men desiring fertility in 6-12 months[99,100]. A prior meta-

Table 1 Characteristics of available testosterone formulations

Formulation	Available strengths	Dose regimen	Advantage	Formulation-specific adverse effects	Monitoring frequency
Parenteral preparations					
Testosterone enanthate	50, 75, 100 mg in 0.5 mL and 200 mg in 1.0 mL sesame oil	Start with 75 mg weekly subcutaneous/intramuscular injections and up-titrate dose to reach target T	Relatively inexpensive, flexible dosing	Pain of injections; fluctuations in symptoms due to peaks and troughs in serum T	50, 75, 100 mg in 0.5 mL and 200 mg in 1 mL sesame oil
Testosterone cypionate	100 and 200 mg/mL in cottonseed oil	Deep intramuscular injection to gluteal muscles once in 2 wk or subcutaneous injections in abdominal adipose tissue weekly		Pain of injections. Fluctuations in symptoms due to peaks and troughs in serum T	50, 75, 100 mg in 0.5 mL and 200 mg in 1.0 mL sesame oil
Testosterone undecanoate	750 mg/3 mL in castor oil	Start with 750 mg deep intramuscular injection deep in the gluteal muscle repeat after 4 wk and then every 10 wk	Infrequent administration	Painful, large-volume intramuscular injection; some report coughing immediately after injection. Possible risk of pulmonary oil micro-embolism	750 mg/3 mL in castor oil
Implants					
Testosterone pellets	75 mg/pellet	Inserted subcutaneously into fat in the hip area; 2 to 6 months will last 3 to 4 months; 6-10 implants last for 4-6 months	Infrequent administration	A surgical incision is required for insertions; local hematoma and infection; spontaneous extrusion of pellets	Measure T concentrations at the end of the dosing interval; adjust the number of pellets and/or dosing interval to maintain serum T concentrations in the mid-normal range
Topical/transdermal					
Testosterone patch	2 or 4 mg patches daily	4 mg starting dose, to be applied to back, abdomen, and upper arms. Do not apply the patch to the same area within 7 d	Easy application	Serum T concentrations are sometimes in the low-normal range. May need applications of two patches daily. Skin irritation at the application site	Assess serum T 3-12 h after application; adjust the dose to achieve T levels in the mid-normal range
Testosterone gel	1.00% gel-50 to 100 mg T/d	25-50 mg T packets to apply to the shoulder or upper arms; 20.25 mg T per 1 pump actuation, or a 20.25 mg packet	Flexibility of dosing; easy application; good skin tolerability; less erythrocytosis	Potential of contact transfer to female partners or children; skin irritation in some	Assess serum T 2-8 h following gel application, after the patient has been on treatment for at least 1 wk; adjust the dose to achieve serum T in the mid-normal range
	1.62% gel-40.5 to 81 mg T/d	40.5 mg T. 2 pump actuation or a 40.5 g packet; apply to shoulders or upper arms			
	2.00% gel 10 mg/0.5 g per pump actuation	40.0 mg (4 pump actuation)/d starting dose; apply to inner thighs			
	2.00% lotion 30 mg/pump actuation	Start with 60 mg, apply to axilla	Good skin tolerability	Potential of contact transfer to female partners or children. Dripping/wet sensation in the axilla	
Buccal/nasal					
Buccal tablets	30 mg twice/d	Apply to gums	Convenience and discreet	Gum-related adverse events; dislodgment	
Nasal gel	11 mg gel intranasal two or three times daily	Start with one actuation (5.5 mg) into each nostril-a total of 11 mg; apply to nose three times daily	Rapid absorption and avoidance of first-pass metabolism	Multiple daily intranasal dosing; local nasal irritation; not appropriate for men with nasal disorders	

Oral					
Testosterone undecanoate capsules	40 mg capsules 2-3 times daily. 158 to 396 mg twice daily	80 to 120 mg/d. Start with 237 mg twice a day with food	Convenience of oral administration	Variable response; must be administered along with a fatty meal; fat content of meals may increase bioavailability	Monitor serum T 3-5 h after ingestion of the tablet

T: Testosterone.

analysis reported, however, that previous TRT did not negatively impact treatment outcomes with gonadotropin/GnRH fertility induction[101].

Cardiovascular risks with TRT

In a retrospective review of men with low T undergoing angiography, TRT was found to be associated with an increased risk of composite CV outcome of MI, stroke and death (HR: 1.29), as also reported in an insurance database-based study [102,103]. However, post-hoc analysis of the AIM-HIGH trial showed low T levels to be associated with an increased risk for primary composite CV outcome in men with MetS and low HDL cholesterol[15]. All observational studies have limitations including heterogeneous study population and differences in treatment regimens, durations, baseline risk factors and study design. One of the first RCTs, designed to investigate functional immobility following TRT in older men with sarcopenia [testosterone replacement for older men with sarcopenia, (TOM trial)], had to be stopped prematurely due to an unexpected increase in CV events with TRT[76].

Subsequent RCTs excluded men with high baseline CV risk. Therefore, most trials reported very few MACEs. However, meta-analyses of several RCTs failed to show a statistically significant association of TRT with CV events[104, 105]. In most of the RCTs, CV events were not a prespecified outcome. Two RCTs-the Cardiovascular Trial of the T Trials and the Testosterone Effects on Atherosclerosis in Ageing Males Trial-reported that the carotid intima-media thickness and the coronary calcium scores did not change with TRT, though there was an increase in the volume of noncalcified plaque with TRT in the former[76,85]. Overall, the FDA notified that these trials have significant limitations that weaken their value. It nevertheless directed pharmaceutical companies to include a label, warning about the cardiovascular risks of TRT. Further trials are ongoing that might lead to more clarifications.

Risks of venous thromboembolism

By stimulating erythropoiesis and increasing hematocrit, TRT runs the theoretical risk for VTE. One case-control study and a registry-based study have demonstrated up to two-fold increased risk of VTE within six months after TRT[106, 107]. However, the number of events was too small, and most cases occurred in men with preexisting hypercoagulable states.

RECOMMENDATIONS ON THE USE OF TRT IN MOSH

The Endocrine Society (ES), European Association of Urologists and Andrologists (EAU, European Academy of Andrology) and the American Association of Clinical Endocrinologists (AACE) recommend TRT to be used in symptomatic hypogonadal men to induce/maintain secondary sex characteristics and to improve symptoms of sexual satisfaction like libido, erectile function, and emotional satisfaction. These guidelines do not recommend TRT for the sole

Table 2 Cautions with testosterone replacement therapy and monitoring for adverse effects

High-risk population for TRT	Special considerations in monitoring
Very high risk of serious outcomes: prostate cancer; breast cancer	For patients who opt for prostate monitoring: Men aged 55-69 yr & those aged 40-69 yr who are at increased risk for prostate cancer and choose monitoring; perform DRE and measure PSA at baseline, at 3-12 months after starting treatment, and then as per local prostate cancer screening guidelines
Moderate to high risk of adverse outcomes	Urologic consultation should be sought if: (1) Increase in serum PSA > 1.4 ng/mL within 12 months of starting TRT; (2) PSA > 4 ng/mL at any time; (3) DRE detected new onset prostate abnormality; and (4) significant worsening of LUTS
Unevaluated prostate nodule or induration	To check Haematocrit at baseline, then at 3-6 months following TRT, and then annually. If Hct > 54%, stop therapy until it decreases to a safer level; evaluate for other causes of erythrocytosis (sleep apnoea, COPD), re-initiate at lower doses when Hct falls below normal
Baseline PSA > 4 ng/mL or > 3 ng/mL in men at high risk for prostate cancer	
Severe lower urinary tract symptoms	
Haematocrit > 48% (> 50% for men living at high altitudes)	
Uncontrolled or poorly controlled heart failure	
Myocardial infarction or stroke in the preceding 6 months	
Untreated severe obstructive sleep apnoea	
Wants fertility in the near future	
Formulation-specific adverse effects (Table 1)	

TRT: Testosterone replacement therapy; PSA: Prostate specific antigen; DRE: Digital rectal examination; Hct: Haematocrit; COPD: Chronic obstructive pulmonary disease; LUTS: Lower urinary tract symptoms.

purpose of weight reduction in obese men, for improved glycemic control or metabolic outcomes in men with MetS or T2DM, to improve exercise capacity, physical functioning, or cognitive functioning in elderly males or as an anti-ageing agent. The recently published SIAMS and SIE guidelines recommend starting TRT in all symptomatic hypogonadal men and older men with hypogonadism for improvement in sexual functioning, to improve BMD and prevent bone loss, to improve major depressive symptoms, to reduce WC and improve body composition and also to reduce fasting and post-load glucose status[11].

The EAU recommends lifestyle changes for weight reduction in overweight and obese men with functional hypogonadism as weight loss can lead to increased serum T. It recommends against TRT for weight reduction in obese men or for glucometabolic outcomes[108]. The AACE and American College of Endocrinology recommend consideration of TRT in men with symptomatic hypogonadism and obesity not for fertility, but only as an addition to lifestyle intervention. These guidelines recommend against TRT in men to improve glycemic control, although they do not make any recommendation for or against TRT for weight reduction. The recent SIAMS and SIE recommend TRT to reduce WC and improve body composition by reducing fat mass and increasing lean mass in subjects with hypogonadism with or without MetS or T2DM[11]. They also recommend TRT to improve fasting and post-prandial glycemia in subjects with hypogonadism with MetS or prediabetes to reduce the risk of progression to T2DM. However, they recommend against considering TRT to control dyslipidemia or to improve HbA1c% in patients with or without T2DM.

Thus, it might be a prudent decision to start TRT in obese men with MOSH, especially if they have dysglycemia. However, if used in the elderly or those at high risk for cardiovascular events, this must be weighed against potential risks and done under close supervision, as outlined in section 8.

AVAILABLE T PREPARATIONS

The available formulations of T, dosing schedule and formulation-specific adverse effects are listed in Table 1. The SIAMS guidelines recommend gel formulation of T for the treatment of older adults with hypogonadism, especially if potentially reversible conditions like obesity are present.

Do different formulations of T have different effects and side effects?

The heterogenous results of TRT from multiple trials lead to speculations about whether the type and route of adminis-

tration of TRT can play a role in this, and this has also been substantiated by sensitivity and meta-regression analyses. The potential for aromatization might explain the heterogeneity in findings, especially the effects on bone density and HDL cholesterol. Observational studies employing the long-acting parenteral TU, indicate a consistent effect of TRT on BMI and central obesity[109]. Both transdermal and parenteral preparations of T have been demonstrated to improve fasting glycemia and body composition. However, no improvement in body composition was observed in trials using oral T preparations. In a study, both transdermal and parenteral T significantly improved FPG. Among the parenteral preparations, TU produced greater reductions in fat mass and lean mass. Transdermal and oral TRT lead to increased serum dihydrotestosterone (DHT) due to increased 5-alpha reductase activity present in the skin and liver. In a study, serum DHT is associated with incident CVD and stroke risks and all-cause mortality[16,110].

Contraindications of TRT

Both the ES and the EAU recommend against TRT in men with prostate or breast cancer or if there is a suspicion of prostatic malignancy in the form of a palpable prostate nodule or palpable induration or a prostate-specific antigen (PSA) level > 3 ng/mL, combined with other risk factors, severe LUTS as evidenced by International Prostate Symptom Score > 19. Other contraindications are listed in Table 2.

MONITORING OF PATIENTS RECEIVING TRT

Monitoring for efficacy

Those on TRT should be assessed for clinical response and adverse effects at the third and twelfth months after initiation and thereafter every year. Biochemical monitoring for efficacy should be done with measurement of serum T at different time intervals while on TRT (Table 2), targeting T levels in the mid-normal range, usually 280-873 ng/dL.

Monitoring for adverse effects

Before initiation of TRT in men > 40 years of age, the potential benefits, and risks along with the need for prostate cancer screening must be discussed, and the patient must be engaged in shared decision-making. This includes all men between 55-69 years of age with life expectancy > 10 years and those between 40-69 years at high risk for prostate cancer. Further details about monitoring of prostate-related adverse effects and haematocrit are outlined in Table 2.

ROLE OF OTHER THERAPEUTIC INTERVENTIONS FOR MOSH

SERMs and AI

AI and SERMs can be an alternative for TRT but have not yet been established as common clinical practice[111]. Due to the worsening of bone density without any improvement of body composition, AIs are not an ideal alternative to TRT in obese hypogonadal men[112].

hCG with TRT

The use of hCG in hypogonadal men is promising, given recent evidence that it stimulates recovery of spermatogenesis from TRT-induced azoospermia[113]. However, the main disadvantage is frequent injections with pain and discomfort. Further studies are needed to provide evidence of improved hypogonadism and erectile function in the setting of non-testosterone-based treatment in patients with MOSH.

CONCLUSION

Treatment of MOSH should involve approaches in an integrated fashion combining lifestyle modifications with TRT. Diet, along with a combination of aerobic and muscle-strengthening exercises, forms the cornerstone of obesity management. Given the effects of TRT on body composition, particularly an increase in muscle mass and strength, TRT facilitates the ability to exercise more. A combination of TRT along with appropriate lifestyle modifications is expected to result in better outcomes. A limited number of studies have, however, addressed this issue. Small RCTs have suggested that a combination of TRT and LSM can lead to improvements in glycemic control, insulin resistance indices, atherogenic lipid profile, blood pressure, body composition, fatty liver indices and even reversal of MetS. Randomised controlled trials comparing the effects of obesity management, TRT and other agents like SERMs on different aspects of MOSH are necessary to make recommendations regarding their pragmatic use. Patients who are on TRT should be regularly monitored as per the current international guidelines to ensure they receive the benefits of therapy and to detect potential complications on time. Prompt selection of the appropriate individuals and optimal management strategies for the underlying conditions including obesity should be planned in curtailing the problems posed by MOSH.

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FOOTNOTES

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