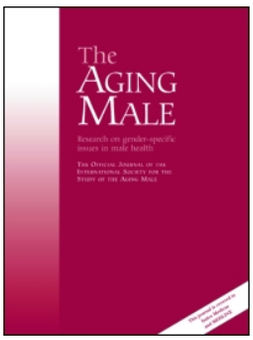

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Monica Caliber & Geoff Hackett

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COMMENTARY

Important lessons about testosterone therapy- weight loss vs. testosterone therapy for symptom resolution, classical vs. functional hypogonadism, and shortterm vs. lifelong testosterone therapy

Monica Caliber[a] and Geoff Hackett[b,c,d]

[a]American Medical Writers Association, Fort Lauderdale, FL, USA; [b]Good Hope Hospital, Birmingham, UK; [c]Department of Urology, Aston University, Birmingham, UK; [d]Heart of England NHS Foundation Trust, Birmingham, UK

ABSTRACT

In this commentary, we highlight important findings from a notable RCT by Ng Tang Fui et al. 2016 which investigated the effects of testosterone treatment in dieting obese men. First, a myopic focus on weight loss can detract from important improvements in body composition. Second, while weight loss in obese men may increase testosterone levels, this increase is commonly not enough to result in an improvement in symptoms associated with testosterone deficiency. Third, the RCT by Ng Tang Fui et al. adds evidence to the growing number of clinical trials showing that testosterone therapy should not be restricted to men with classical hypogonadism. Finally, the beneficial effects of testosterone therapy are not maintained after cessation of treatment. Currently, the British Society for Sexual Medicine guidelines are the only clinical guidelines which acknowledge that weight loss *per se* does not automatically translate to resolution of hypogonadal symptoms, that testosterone therapy can greatly benefit men with testosterone deficiency who do not have classical hypogonadism, and that cessation of testosterone therapy causes reappearance of symptoms and reversal of benefits. Lifelong testosterone therapy is therefore recommended for persistent health benefits in most men with testosterone deficiency. Physicians and patients need to be informed of this.

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Obesity; weight loss; body fat; lean body mass; testosterone deficiency; testosterone treatment; symptoms

Introduction

We applaud Ng Tang Fui et al. [1] for their randomized controlled trial investigating the effects of testosterone therapy or placebo together with caloric restriction and moderate intensity exercise on body composition outcomes. Men aged 18–70 years with low testosterone were randomly allocated to receive 1000 mg testosterone undecanoate injections or placebo injections at weeks 0 and 6, and every 10 weeks thereafter throughout the 56-week study. During weeks 1–8, all subjects followed a very low energy diet (VLED, also known as "very low-calorie diet") providing 640 calories per day and two cups of low-starch vegetables. During weeks 9–10, subjects weaned their VLED and ordinary foods were gradually reintroduced. After 10 weeks, subjects had completely ceased the VLED and were instructed to follow an energy-restricted diet providing 1350 calories per day, aimed at preventing weight regain, for the remaining 46 study weeks. Subjects were advised to perform at least 30 min of moderate-intensity exercise each day and completed exercise questionnaires and accelerometer testing (at weeks 0, 10, and 56) to reinforce and encourage participation in exercise. The results were reported as mean adjusted differences (MAD), calculated as the difference between groups of mean change in the outcome measures over time. DEXA and computed tomography were used for body composition and visceral fat assessment [1].

After the acute VLCD, no significant between-group differences were seen for any of the measured outcomes, but the testosterone-treated group showed numerically larger reductions in fat mass and visceral fat, and a smaller reduction in lean body mass (LBM), compared to the placebo group [1]. After 56 weeks, the testosterone-treated group had lost significantly more fat mass (−2.9 kg, $p = .04$), fat mass percentage (−2.8%, $p = .003$) and visceral fat (measured by computed tomography, −27 cm^2, $p = .04$), and regained the acute diet-induced loss of lean mass (3.4 kg, $p = .002$), compared to the placebo group [1]. Changes in body mass were not significant at either time point. At

CONTACT Monica Caliber m@MonicaCaliber.com American Medical Writers Association, Fort Lauderdale, FL, USA

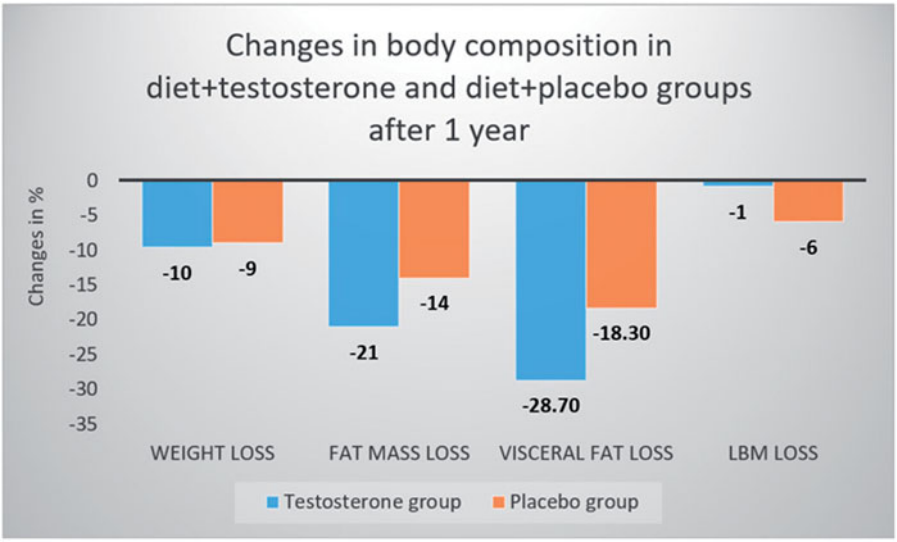

Figure 1. Changes in body composition and total body mass at 56 weeks after an initial 10 weeks of a very low-calorie diet followed by 46 weeks of an energy restricted diet (1350 Kcal/d) [1]. LBM: lean body mass.

study end, the combined LBM and fat mass reduction in the placebo group were similar in magnitude to the fat mass reduction in the testosterone group, which explained why there was no difference in body mass change between the two groups at the end of the study (Figure 1) [1].

Reduction in visceral fat mass

Notably, the greater reduction in visceral fat by 27 cm^2 in the testosterone group compared with placebo is of larger magnitude than that seen after 22 weeks of aerobic training, resistance training or both combined (–11, –8, –20 cm^2, respectively), all of which resulted in improvements in glycemic control [2]. A longer 52-week aerobic exercise intervention trial (same duration as the study by Ng Tang Fui et al. [1]) found a reduction in visceral fat (assessed by CT) of only 12 cm^2 [3]. Other clinical trials have also demonstrated that testosterone therapy reduces visceral fat mass and/or waist circumference [4–6], and prevents the gain of visceral fat mass over time [7].

Weight loss vs. body composition improvement

Obesity treatment interventions, such as caloric restriction, commonly target weight loss alone [8–10], without attention to intervention effects on body composition and health outcomes [11–15]. As shown in the study by Ng Tang Fui et al. [1], a myopic focus on weight loss alone can mask important body composition improvements. This is unfortunate as it can lead to frustration and drop-out among patients who think that weight loss is the only desirable result.

Effect of testosterone therapy on the preservation of lean body mass during a hypocaloric diet – importance of achieving high enough physiological testosterone levels

In the RCT by Ng Tang Fui et al. it should be noted that the post-VLCD energy-restricted diet providing 1350 calories per day was relatively stringent, considering that the estimated Harris-Benedict basal energy requirement to support even the lowest body weight subjects weighing 90 kg is 2200 calories [16]. This degree of caloric restriction likely contributed to the large loss of LBM in the placebo group. Nevertheless, the negative energy balance was the same in both groups.

The lack of effect of testosterone therapy on preventing the loss of LBM during the 10-week VLCD weight loss phase was explained by Ng Tang Fui et al. as possibly attributable to the short 10-week treatment duration. We would like to raise the question; would it be possible to prevent the loss of lean mass by achievement of a higher – yet safe - physiological testosterone level? The increase in testosterone levels in testosterone-treated men from a mean baseline level of 8.2 nmol/L (237 ng/dL) to 19 nmol/L (548 ng/dL) at week 10 and 15.6 nmol/L (450 ng/dL) at study end (week 56) may possibly have been too small to prevent loss of lean mass during calorie restricted dieting.

Because gains in lean mass and skeletal muscle mass are associated with testosterone dose and

achieved serum testosterone levels [17–20], it is likely necessary to raise testosterone levels higher than 15.6 nmol/L to realize clinically meaningful gains in LBM – a large portion of which is skeletal muscle mass (SMM) - or prevent its loss during calorie restriction. In addition, what constitutes a clinically meaningful gain in SMM or LBM also needs to be clarified, and both physical function [21,22] and metabolic parameters [23,24] considered.

In another study, men aged 62–72 year with a baseline testosterone level at the low end of the normal range (12.5 nmol/L–361 ng/dL) and a waist circumference of >94 cm, body weight of 92 kg and BMI of 30, were given testosterone therapy that elevated testosterone levels to the mid-normal range (18.7 nmol/L–539 ng/dL) at month 3 and 22.2 nmol/L (640 ng/dL) at month 6 resulted in a significant increase in LBM of 1.8 kg (+3%) after 3 months (lean mass did not increase further at month 6 in this study), compared to placebo [25]. If testosterone therapy can result in a significant increase in lean mass after 3 months (12 weeks), it is plausible that further elevating testosterone levels with higher doses of testosterone supplementation may have the capacity to prevent loss of lean mass during a hypocaloric diet of similar duration.

A notable dose-response study by Bhasin et al. gave 60 ambulatory healthy older men aged 60–75 year, with low testosterone levels, a GnRH agonist (to suppress endogenous testosterone production) and 25, 50, 125, 300, or 600 mg testosterone enanthate weekly for 20 weeks [19]. Baseline testosterone levels were between 10.8 nmol/L (312 ng/dL) and 13.4 nmol/L (387 ng/dL), and testosterone treatment resulted in final testosterone levels (at week 16) of 6.1 nmol/L (176 ng/dL), 9.5 nmol/L (274 ng/dL), 29.5 nmol/L (852 ng/dL), 61.9 nmol/L (1784 ng/dL) and 113.9 nmol/L (3286 ng/dL), respectively. Men in the groups achieving testosterone levels of 29.5 nmol/L (852 ng/dL), 61.9 nmol/L (1784 ng/dL), and 113.9 nmol/L (3286 ng/dL) had gains in fat free mass (FFM) of 4.2, 5.6, and 7.3 kg, respectively (measured by DEXA). Similar changes were noted in young men (19–35 year) [19]. In a separate analysis of the Bhasin et al. dose-response study, the groups that achieved nadir testosterone levels of 852 and 1784 ng/dL after 20 weeks of testosterone treatment had a significant increase in skeletal muscle mass of 8.5% and 11.1%, respectively [17]. It should be noted that the skeletal muscle mass data in the second study was derived from the appendicular lean tissue mass, which is not synonymous with FFM or LBM [17]. Nevertheless, the data support the hypothesis that it is likely necessary to raise testosterone levels to the mid or higher end of the physiological range in order to realize clinically meaningful gains in LBM (or muscle mass, depending on how it is measured), or prevent its loss during a diet. These studies clearly demonstrate a dose-response effect between achieved serum testosterone level and lean mass gains. It is possible that a similar dose-response effect exists for prevention of lean mass loss during a hypocaloric diet. This warrants further study.

In addition to the reported testosterone dose-related changes in FFM in older and younger men, the study by Bhasin et al. also found a dose-response for fat mass loss; changes in fat mass were inversely associated with testosterone dose as well as total ($r = -0.50$; $p < .001$) and free ($r = -0.48$; $p < .001$) testosterone levels in older men [19]. Interestingly, emerging RCT data by Dhindsa et al. suggest that testosterone treatment may also reduce body fat and increase LBM in non-dieting obese men [26]. Not surprisingly, the changes in LBM and subcutaneous fat mass in the testosterone group were inversely related ($r = -0.47$, $p = .05$) [26].

Risk-to-benefit ratio of testosterone treatment

Importantly, the dose-response study by Bhasin et al. also provides valuable insights on the risk-to-benefit ratio of testosterone treatment [19]. Treatment was discontinued because of serious adverse events in three older subjects achieving the supraphysiological testosterone level of 113.9 nmol/L (3286 ng/dL) and in three achieving 61.9 nmol/L (1784 ng/dL), after having been treated with 300 or 600 mg testosterone enanthate weekly for 20 weeks, respectively. In the 113.9 nmol/L (3286 ng/dL) group, treatment was discontinued due to hematocrit exceeding 54%, hematuria and urinary retention, or because of leg edema. One additional subject stopped treatment after the Data Safety Monitoring Board discontinued the 600 mg/week dosing arm in older men because of a high frequency of serious adverse events. This is not surprising as 113.9 nmol/L (3286 ng/dL) is clearly a highly supraphysiological testosterone level. Three men in the 61.9 nmol/L (1784 ng/dL) group (300 mg/week) were discontinued from the study because of hematocrits above 54% in all three plus, leg edema in one and PSA above 4 μg/ml in another. Two older men were diagnosed with prostate cancer; one man in the 1784 ng/dL group underwent biopsy because of a PSA level greater than 4 μg/ml, and a second man in

the 274 ng/dL group. Notably, there was no MACE (Major Adverse Cardiovascular Events) reported [19].

The group of older men achieving a mean physiological testosterone level of 852 ng/dL after suppression of endogenous testosterone and weekly injections of 125 mg of testosterone enanthate for 20 weeks had no serious adverse events, a low frequency of adverse events, and substantial gains in fat free mass (+4.2 kg) and leg press strength (+28 kg) as well as a significant 1.5 kg reduction in body fat [19]. These data support the hypothesis that therapeutic testosterone doses that elevate testosterone levels to the mid-range of normal may further increase the loss of fat mass in obese hypogonadal men undergoing severe caloric restriction.

Efficacy and safety were demonstrated in two other dose-response studies that achieved testosterone levels of 900 ng/dL or higher [18,20,27]. A recent small RCT in healthy men, aged 25–55 years, with normal serum total testosterone levels showed that treatment with high dose testosterone gel (up to 15 g per day) for 12 weeks - achieving testosterone levels of 1150 ng/dL (40 nmol/L) - did not adversely affect lipids, glucose or insulin, while resulting in the expected dose-dependent increase in LBM and decrease in fat mass [20]. Impact on hematocrit and PSA was not reported. A 6-month RCT by Dhindsa et al. demonstrated the safety of achieving serum testosterone levels of 780 ng/dL (by treatment with 250 mg testosterone cypionate every 2 weeks for 24 weeks) [26]. Likewise, the 3 year long testosterone RCT by Basaria et al. – the longest RCT to date – showed that achieving a testosterone level of 22.5 nmol/L (650 ng/dL) is safe [28].

While preliminary data suggest that a serum testosterone level in the range of 27.7–31.2 nmol/L (800–900 ng/dL) - almost twice as high as the testosterone level achieved in the study by Ng Tang Fui et al. [1] – may provide the best tradeoff between beneficial anabolic and fat loss effects, and adverse events, there are not enough safety data to support a target testosterone level of 800–900 ng/dL. On the other end, as shown by Ng Tang Fui et al. [1], 450 ng/dL may be too low to prevent loss of LBM during a negative energy balance. Aiming for a target testosterone level that was achieved in the 3 year RCT by Basaria et al., 22.5 nmol/L (650 ng/dL), seems to be the most sensible approach to potentially realize a greater beneficial impact on body composition outcomes.

Improvement in hypogonadal symptoms

A second report of the diet study by Ng Tang Fui et al. found that only testosterone-treated patients had improvements in hypogonadal symptoms [29]. While weight loss in obese men does increase testosterone levels, the amount of weight loss that can be realistically achieved and maintained with diet and exercise is likely not large enough to translate into sustained symptomatic improvement. This was shown in a study of the Diabetes Prevention Program, which examined the effect of an intensive lifestyle intervention on changes in testosterone and mood among middle-aged men [30]. The intensive lifestyle intervention, which resulted in a weight loss of 7.97 kg after 1 year, increased endogenous testosterone from 10.98 nmol/L to 12.13 nmol/L (+1.15 nmol/L, 10% increase). However, there was no significant improvement in mood. This is not surprisingly considering that the testosterone elevation was quite small (despite the intensive lifestyle intervention). In the EMAS study, spontaneous resolution of secondary hypogonadism was accompanied by a 45% increase in testosterone levels, from 9.2 nmol/L at baseline to 13.3 nmol/L), but this was still not sufficient to drive improvements or resolution of sexual symptoms [31]. It seems like at least a 2-fold increase of testosterone levels into the mid-normal physiological range is required for symptomatic improvements, which has been demonstrated in randomized controlled trials of testosterone therapy showing improvements in sexual function [32], physical strength [33], and depressive symptoms [34].

Notably, the British Society for Sexual Medicine Guidelines on Adult Testosterone Deficiency underscores that lifestyle modification and weight loss alone have failed to demonstrate effective improvement in clinical symptoms, even after more than 4 years, and that patients need to be informed of this [35]. Considering that symptomatic improvements will most likely contribute to adherence with diet and exercise programs, one can question the validity of using weight reduction alone as the primary outcome variable.

Functional hypogonadism vs. classical hypogonadism

It should also be pointed out that the RCT by Ng Tang Fui et al., and numerous other controlled trials [4–6,36] showing that testosterone therapy significantly improves body composition, all included men with functional hypogonadism. Men with functional hypogonadism are typically middle-aged and older men (>50 years-old) – many of whom are obese and suffer from comorbidities such as the metabolic

syndrome, diabetes or dyslipidemia – and commonly present with clinical features consistent with androgen deficiency and reduced testosterone levels [37]. These men, which constitute the large majority of suffering hypogonadal men, do not have anatomical hypothalamic-pituitary-testicular axis pathology characteristic of classical hypogonadisms [37]. Notably, these data, along with the Testosterone Trials data [38], refute the traditional view that testosterone treatment should be restricted to men with classical hypogonadism (primary or secondary hypogonadism caused by specific, well-recognized medical conditions, such as Klinefelter's syndrome, pituitary injury, or toxic damage to the testicles) [39], by showing that men with hypogonadism – regardless of etiology – significantly benefit from testosterone treatment. Accordingly, both the BSSM guidelines and an international expert consensus have concluded that the symptoms and signs of testosterone deficiency occur as a result of low testosterone levels and may benefit from treatment regardless of whether there is an identified underlying etiology, and that no evidence exists to support the restriction of testosterone therapy only to men with known underlying etiology [35,40].

Shortterm vs. lifelong testosterone therapy

A third report of the diet study by Ng Tang Fui et al. assessed whether body composition changes are maintained following the withdrawal of testosterone treatment [41]. At the end of the observation period, 82 weeks after the termination of treatment with either testosterone or placebo, the previous between-group differences in fat mass, lean body mass were no longer seen. It was concluded that the beneficial effects of testosterone therapy on body composition in men undergoing a concomitant weight loss program were not maintained at 82 weeks after testosterone treatment cessation [41].

Several other studies have also demonstrated that the beneficial effects of testosterone therapy are not maintained after cessation of treatment [42–47]. This applies not only to improvements in body composition, but also improvements in erectile function, HbA1c, total cholesterol, LDL, HDL, triglycerides, AMS, IPSS, IIEF-EF, residual voiding volume and bladder wall thickness, and quality of life, and likely most – if not all - other testosterone-related outcomes [42–45,47]. If testosterone therapy is discontinued, beneficial effects return when testosterone therapy is resumed [42].

As pointed out in the British Society for Sexual Medicine guidelines on Adult Testosterone Deficiency, cessation of testosterone therapy results in the reappearance of symptoms and reversal of benefits within 6 months, so testosterone therapy is likely to be required lifelong for persistent symptom resolution and maintenance of health benefits [35].

Conclusion

In conclusion, achieving higher testosterone levels during testosterone treatment – albeit still within the safe therapeutic range – may not only prevent loss of lean mass but also possibly contribute to a greater loss of fat mass in the context of a negative energy balance. Further research is warranted to specifically examine the dose-response effects of testosterone treatment on body composition outcomes in conjunction with calorie-restricted diets, as well as during eucaloric conditions.

The RCT by Ng Tang Fui et al. [1] contributes important evidence to the growing number of studies showing that testosterone therapy should not be restricted to men with classical hypogonadism; all men with testosterone deficiency, regardless of cause, safely benefit from testosterone therapy. Ng Tang Fui et al. furthermore provides excellent data showing that weight loss alone – if it is achieved – does not automatically translate to the resolution of hypogonadal symptoms. Ng Tang Fui et al. additionally confirms previous findings that upon termination of testosterone therapy the benefits are not maintained. Lifelong testosterone therapy with regular monitoring to ensure normalization of testosterone levels, i.e. achievement of high enough safe physiological testosterone levels, is therefore likely necessary.

Currently, the BSSM guidelines are the only clinical guidelines which provide guidance on these three aspects of testosterone therapy; weight loss vs. testosterone therapy for symptom resolution, classical vs. functional hypogonadism, and shortterm vs. lifelong testosterone therapy. We hope this commentary will help health care professionals make more informed decisions and provide better care for their obese patients with hypogonadism.

Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

Monica Caliber http://orcid.org/0000-0003-3057-7313

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