Introduction

Obesity is a public health threat and is reaching epidemic proportions worldwide with profound impact on overall health, reduced quality of life and premature death (1).

A long-term change in lifestyle including diet and physical activity remains a cornerstone of obesity treatment. It should be noted that behavioral and life style changes such as dieting bring about modest and marginal weight loss (2). This approach is often associated with loss of muscle mass, which may be circumvented by combining diet with exercise. Lifestyle interventions produce significant weight loss, but this weight loss is not sustainable over long time periods and considerable weight regain is noted (3-5).

More than 80% of obese individuals, even if they were highly motivated, remained unable to lose weight or maintain weight loss with dietary and lifestyle modifications alone (6). Thus, achieving long-term, modest weight loss with behavior modification therapy alone is limited, at best, necessitating exploring pharmacotherapy for weight loss. The pharmacological approach to treatment of obesity is hotly pursued, but thus far, only modest changes in weight loss are reported. A number of pharmaco-therapeutic agents have been approved by the Food and Drug Administration (FDA) for the treatment of obesity over the course of the past 20 years. These drugs are designed to alter metabolism and/or to suppress appetite. Nevertheless, for many of these agents the success rate is very small and may produce undesirable adverse effects. It should be noted that many of these pharmaco-therapeutic agents may be associated with cardiovascular or depressive side effects (7) and a number of them have been withdrawn from the market.

Testosterone (T) plays a critical role in regulating energy utilization including nitrogen retention, carbohydrate and fat metabolism and adipogenesis (8). Reduced T levels were recorded in a substantial proportion of obese and diabetic men. Dhindsa et al. were the first to demonstrate a high prevalence (33%) of hypogonadism in unselected male patients with type 2 diabetes (9), and later confirmed in a large number of men that a higher percentage of obese diabetic men were hypogonadal (10). T treatment of obese subjects produced marked increases in lean body mass and reduction in fat mass with improvement in insulin sensitivity (11). T treatment in hypogonadal

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Long-Term Treatment of Hypogonadal Men with Testosterone Produces Substantial and Sustained Weight Loss

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Objective: This study analyzed the effects of normalization of serum testosterone (T) levels on anthropometric parameters in hypogonadal men.

Design and Methods: Open-label, single-center, cumulative, prospective registry study of 255 men (aged 33-69 years, mean 58.02 ± 6.30 years), with T levels below 12.13 nmol/L (mean: 9.93 ± 1.38). 215 men for at least 2 years, 182 for 3 years, 148 for 4, and 116 for at least 5 years were studied. They received parenteral T undecanoate 1,000 mg/12 weeks after an initial interval of 6 weeks.

Results: Body weight (BW) decreased from 106.22 ± 16.93 kg to 90.07 ± 9.51 kg. Waist circumference (WC) reduced from 107.24 ± 9.14 cm to 98.46 ± 7.39 cm. BMI (m/kg²) declined from 33.9 ± 5.51 m/kg² to 29.13 ± 3.09 m/kg². All parameters examined were statistically significant with P < 0.0001 versus baseline and versus the previous year over 5 years indicating a continuous weight loss over the full observation period. The mean per cent weight loss after 1 year was 4.16 ± 0.31%, after 2 years 7.54 ± 0.32%, after 3 years 9.23 ± 0.33%, after 4 years 11.42 ± 0.35% and after 5 years 13.57 ± 0.37%.

Conclusions: In an uncontrolled, observational cohort, normalizing serum T to normal physiological levels produced consistent loss of BW, WC, and BMI. These improvements were progressive over the full 5 years of the study.

men had positive effects on a number of parameters of cardiovascular health, such as serum LDL-cholesterol, blood pressure, and heart rate [reviewed in (10-12)].

In the 1990s, Per Björntorp was among the first to recognize the important role of hormones in obesity (13), especially abdominal obesity. In centrally obese individuals, there is an over-activity of the corticotropin-releasing-hormone (CRH) – corticotropin (ACTH) – cortisol axis. Björntorp hypothesized that this increased activity results in a suppression of the production of T and growth hormone. It was Björntorp’s group that did the first studies using T in obese men, and despite using suboptimal T preparations, they found a decrease in waist–hip ratio, visceral fat mass and an increase in energy. The authors suggested that the elements of energy imbalance, including physical inactivity, stress, smoking, and alcohol consumption are frequent features of modern, urbanized society. Visceral obesity may therefore be an expression of a “Civilization Syndrome” (13).

Significant improvement in body composition was noted in several studies with T treatment (11,14-16). Evidence exists suggesting that T regulates adipogenesis and therefore increases lean body mass and reduces fat mass thus regulating body composition (17-22).

In a registry study of 255 of hypogonadal men seeking urological consultation in a single urologist’s office for various medical conditions, we report on the effects of T treatment for up to 60 months on body weight (BW), waist circumference (WC), and BMI in adult hypogonadal men. The study was not designed to induce weight loss or to treat obesity.

Methods and Procedures

We performed a cumulative registry study of 255 mainly elderly men, aged between 33 and 69 years (mean 58.02 ± 6.30). All subjects had sought urological consultation in a single urologist’s office for various medical conditions; for example, erectile dysfunction, decreased libido, questions about their T status, or a variety of urological complaints. A number of subjects, for instance, men with osteoporosis, had been referred by other specialists with a suspicion of T deficiency. Upon clinical and laboratory investigation, the subjects were found to have subnormal plasma total T levels (mean: 9.93 ± 1.38; range: 5.89-12.13 nmol/L) as well as at least mild symptoms of hypogonadism assessed by the Aging Males’ Symptoms scale. All men received treatment with parenteral T undecanoate 1,000 mg (Nebido®, Bayer Pharma, Berlin, Germany), administered at baseline and 6 weeks and thereafter every 12 weeks for up to 60 months.

Although there is no international consensus as to the normal range of testosterone, clinical data suggest that the normal range of T in adult men is between 12 and 40 nmol/L (23). A threshold of 12.1 nmol/L was recently confirmed by Bhasin et al. (24), in an analysis of a number of important studies such as Framingham Heart Study generations 2 and 3, European Male Aging Study (EMAS), and the Osteoporotic Fractures in Men Study.

Measurements of anthropometric parameters were performed at baseline (height, weight, WC) and at each visit (weight, WC) and blood samples drawn at each visit and prior to the next injection of testosterone. Therefore, T levels were trough levels at the end of an injection interval. WC was measured midway between the upper hip bone and the uppermost border of the right iliac crest. T was measured by standard laboratory measurement. Due to the cumulative registry design of the study, the number of subjects decreased over time. New subjects are entered into the database once they have received one year of treatment with T. All 255 subjects were followed for at least one year, 215 for at least two years, 182 for three years, 148 for four years, and 116 for five years. The declining number of patients reflects duration of treatment but not drop-out rates. On the contrary, adherence to treatment was excellent, and T was only discontinued in three men.

Statistical analyses

For continuous variables, the mean, median, standard deviation, range, minimum, maximum, and sample size for the overall sample and various groups was reported at each time point. For categorical variables, the frequency distribution was reported. We tested the hypotheses regarding change in outcome scores across the study period by fitting a linear mixed effects model to the data. Time (to indicate follow-up interviews) was included as fixed effect in the model. A random effect was included in the model for the intercept. Estimation and test of change in scores were determined by computing the differences in least square means at baseline versus the score at each follow-up interview. For the correlation study, Pearson correlation was calculated between baseline changes in outcomes at various time points. The significance of each correlation was tested using Fisher’s test.

Results

As shown in Table 1, the distribution of subjects based on BMI was: 13 men (5.1%) had normal weight (BMI ≤ 24.9), 61 men (23.92%) were overweight (BMI 25-25.9), 181 men (70.98%) were obese (BMI ≥ 30). In this latter subgroup, 145 men (56.86%) were obese (BMI 30-39.9) and 36 men (14.12%) were excessively obese (BMI ≥ 40). The distribution based on WC was: 11 men (4.31%) had normal WC of <94 cm, 70 men (27.45%) had WC of 94-101.9 cm, and 174 men (68.24%) had WC greater than 102 cm. Almost all men had known comorbidities at baseline (Table 1).

Total testosterone levels during the 60-month period of testosterone treatment

Figure 1 shows total T levels in hypogonadal men treated with T for up to 60 months. Total T levels show a significant rise from approximately 9.9 nmol/L at beginning of therapy to about 18 nmol/L within the first 12 months of therapy, and such physiological levels remain constant at this level throughout the course of treatment.

Treatment of hypogonadal men with testosterone produced reduction in WC

Figure 2A shows the reduction in WC. WC declined from 107.24 ± 9.14 cm (min 86, max 129) to 98.46 ± 7.39 cm (min 84, max 117) with a mean reduction of 8.5 ± 0.17 cm. The reduction in WC was statistically significant at the end of each year compared to the previous year ($P < 0.0001$) over the full 5-year observation period. Approximately 97% of all men in this study showed a decrease in WC.

WC decreased by ≥ 5 cm in 86% of men and by ≥ 10 cm in 46% of men. Approximately 7% of men had a decrease in WC by ≥ 15 cm and only 3% had an increase in WC (Figure 2B).
Treatment of hypogonadal men with testosterone produced significant weight loss (WL)

Figure 3A shows the effects of T therapy on BW in hypogonadal men over the course of 5 years. Weight decreased from 106.22 ± 16.93 kg (min 70, max 139) to 90.07 ± 9.51 kg (min 74, max 115) with a mean loss of 15.35 ± 0.43 kg. This decrease in BW was statistically significant at the end of each year compared to the previous year \( (P < 0.0001) \) over the full 5-year observation period. We note that 31% of men lost ≥10 kg, 53% of men lost ≥15 kg, 76% of men lost ≥10 kg and 90% lost ≥5 kg over the 60 month period of T treatment (Figure 3B). Approximately 5% of men gained weight.

Percentage change in BW as a result of treatment of hypogonadal men with testosterone

Marked and significant decrease in percentage BW was noted over the course of T treatment. Over the entire observation period, patients lost 13.57% of their initial BW (Figure 4A). After 1 year, patients had lost 4.16 ± 0.31% of their initial weight, after 2 years, 7.54 ± 0.32%, after 3 years, 9.23 ± 0.33%, after 4 years, 11.42 ± 0.35%, and after 5 years, 13.57 ± 0.37%. These changes were statistically significant at the end of each year compared to the previous year \( (P < 0.0001) \) over the full 5-year observation period. When correlating per cent weight change with baseline T we found weak but statistically significant and persistent correlation across the 5 years of follow-up (Figure 4B).

Treatment of hypogonadal men with testosterone produced significant decline in BMI

Consistent and progressive decline in BMI was observed over the entire course of treatment (Figure 5). BMI declined from 33.9 ± 5.51 to 32.42 ± 4.87 after 1 year, 31.27 ± 4.6 after 2 years, 30.56 ± 4.13 after 3 years, 30.17 ± 3.79 after 4 years, and 29.13 ± 3.09 after 5 years. The decline in BMI is consistent with the observed reductions in WC and weight.

The data were further analyzed to determine the frequency of changes in BMI in men who were obese or overweight at baseline.
The frequency of changes in BMI was more demonstrable in obese men over time. When the data were analyzed in men who were considered normal based on the BMI at baseline and compared to those who were obese, a marked frequency change is noted in the obese individuals over time (Figure 6A). Clearly, the reduction in BMI in the obese group is remarkable followed by the overweight group but with minimal changes in the normal BMI group (Figure 6A). When the per cent changes in BMI were analyzed in all three groups, there is considerable and marked decrease in BMI over time, which was correlated with baseline T (data not shown). Furthermore, when the changes in weight were analyzed in the three subgroups, the most profound reduction in weight was found in obese men followed by overweight men (Figure 6B). Only men with normal weight at baseline showed a moderate increase in weight.

It should be noted that among those subjects (n = 16) who gained weight, 12 subjects had Crohn’s disease, 2 had ulcerative colitis, 1 had leukemia, and 1 had Hodgkin’s lymphoma. The weight gain in these subgroups may be attributed to attenuation of inflammation in Crohn’s disease and ulcerative colitis with concomitant restoration of muscle mass. Of these 16 patients who gained weight, 9 had a reduction in WC.

The most dramatic weight loss up to 32 kg and reduction in WC of up to 18 cm was observed in a subgroup (n = 36) of subjects with excessive obesity. This observation suggests that T reverses and/or inhibits adipogenesis and restores or promotes myogenesis, thus resulting in the observed dramatic WL, which is paralleled by decreased WC and also reduced BMI in this subgroup.

Eighty men (31% of the total cohort) had type 2 diabetes. Of these, 71 men were obese. A subgroup analysis was performed revealing that in these 71 obese type 2 diabetic patients T treatment reduced fasting glucose from 6.61 ± 0.77 mmol/L (119.07 ± 13.89 mg/dl)
to 5.42 ± 0.16 mmol/L (97.63 ± 2.83 mg/dl), p < 0.0001. Data on HbA1c were available for 55 subjects. HbA1c declined from 8.33 ± 0.78% to 5.88 ± 0.4% (p < 0.0001) in response to T treatment.

Discussion

Here, we demonstrate that testosterone treatment of hypogonadal men produced significant and marked weight loss in approximately 95% of all patients. The WL resulting from T treatment was gradual and sustainable. The WL was significant and associated with marked reductions in WC and BMI, suggesting that T treatment produced changes in body composition, consistent with the reported increase in lean body mass and decrease in fat mass (reviewed in 11). The reductions in WC and BMI were also remarkable with T treatment over the entire observation period of 60 months. The magnitude of changes over time was most notable in the excessively obese and obese and less noted in the group with normal BMI. These findings suggest that T is a physiological modulator of body composition due to its role in promoting myogenesis and inhibiting adipogenesis and its role in carbohydrate, lipid and protein metabolism. The findings of this study were unexpected and accidental as it was not designed to investigate the effects of T on weight loss in hypogonadal men.

FIGURE 6 Effects of testosterone treatment on long-term changes in body composition. Panel A: Changes in proportions of patients in the categories normal weight, overweight, and obese. Panel B: Changes in weight loss in patients in the categories normal weight, overweight, and obese. Dark bars represent patients with normal weight (BMI ≤ 24.9 kg/m²), white bars overweight patients (BMI 25 – 29.9 kg/m²), hatched bars obese patients (BMI ≥ 30 kg/m²).
T production is suppressed by adipose tissue and T levels are reduced in obese men (reviewed in 11). In a study of 2165 men, in the USA, presenting to doctors' offices, the prevalence of T deficiency (TD) in obese men was 52.6% (25). Corona et al. (26) reported on 1687 men presenting to an outpatient andrology clinic in Italy for sexual dysfunctions, the prevalence of hypogonadism was 29.3% in obese men. In all reported studies to date, T treatment consistently showed decreased fat mass and increased lean body mass. However, in short-term studies minimal or moderate effect on weight was recorded [19-22]. The studies with the longest duration in the literature were at best 3 years duration (11). In one of those studies, a placebo-controlled pilot study in men treated for 3 years with T undecanoate, WC declined by 13 cm (15).

Epidemiological evidence from several longitudinal population studies shows that low T is an independent risk factor for the development of both metabolic syndrome (MetS) and type 2 diabetes (T2DM), stroke, or transient ischemic attacks. T levels are reduced in men with T2DM, with an inverse association between T levels and glycosylated hemoglobin (HbA1c). An inverse relationship between indicators of obesity (BMI, WC, a reliable indicator of visceral obesity), and T levels over all age groups has been reported (12). Men with features of the MetS exhibit reduced T levels and T treatment in such individuals positively affects weight reduction, with concomitant reduction in insulin resistance (27).

In our study, the marked weight loss observed in this cohort of hypogonadal men treated with T may be explained by changes in the metabolism in response to T treatment. It is well known that T regulates energy utilization via multiple cellular metabolic pathways, including nitrogen retention, carbohydrate, and fat metabolism and regulation of adipogenesis (10,12). T also regulates lineage of mesenchymal pluripotent cells by promoting the myogenic lineage and inhibiting the adipogenic lineage (28). T also inhibits triglyceride uptake and lipoprotein lipase activity resulting in rapid turnover of triglycerides in the subcutaneous abdominal adipose tissue and mobilizes lipids from the visceral fat depot. Thus, the findings of this study can be explained, in part, by the increase in lean body mass and reduction in fat mass attributed to changes in metabolism modulated by T treatment. In addition, T treatment increases motivation, enhances mood, and promotes more active lifestyle, thus preparing the body for physical activity and increased energy expenditure, thus contributing to further weight loss.

Hypogonadism is known to be associated with reduced motivation and loss of energy. In an observational study of more than 1,400 hypogonadal men from 155 centers in 23 countries receiving 1 year of T treatment (IPASS), it was shown that the overall level of vigor/vitality was markedly increased (29). This, together with increased quality of life, may explain, in part, the increase in physical activity associated with T treatment (30). The increased motivation, level of energy, and vigor associated with T treatment may explain the reduction in BW due to increased energy expenditure.

It is well recognized that mitochondria play a critical role in regulating lipid, protein, and carbohydrate metabolism (31). The increased energy utilization via oxidative phosphorylation is attributed to the effect of T on the mitochondrial function. T upregulates a host of enzymes and transcriptional factors important in metabolic function, especially in the mitochondria (31). Thus, the effects of T on mitochondrial function may represent a novel mechanism in modulating increased energy utilization and regulation of insulin sensitivity, body composition and weight loss.

In our registry, the cohort of 255 patients investigated with mean age of 58 years treated with T for 60 months, only 3 patients were diagnosed with prostate cancer. This incidence represents 1.2% [95% CI (0.24-3.4%)] and an incidence of 30.3 [95%CI (0.9783-9.4052)] per 10,000 person years. Andriole et al. [32] showed that in the prostate, lung, colorectal, and ovarian cancer screening trial (PLCO) in which 38,345 men ages 55-74 years in the control arm were followed up to 13 years, 3,815 men were diagnosed with prostate cancer representing an incidence of 97.1 per 10,000 person-years. In The European Randomized Study of Screening for Prostate Cancer (ERSPC) of 72,891 patients, mean ages 55-69 year, and a follow up of 11 years showed that 6,963 patients were diagnosed with prostate cancer (9.6%) and an incidence of 96.6 per 10,000 person years [33]. On the basis of the results from these extensive screening trials, the incidence of prostate cancer in our cohort remained lower than expected. T treatment in men did not exacerbate voiding symptoms due to benign prostatic hyperplasia (34) and recent reports placed such fears on prostate cancer in a more rational perspective (35-37).

To date, there is no convincing evidence that T is the main factor in the development or progression of prostate cancer in men (37) and guidelines for monitoring have been developed, which, if properly applied, render T treatment to be a safe therapy in men without suspicion of prostate carcinoma.

One of the limitations of this study is the nature of the registry design. This single-center, open-label study is not a randomized controlled study and therefore limits the scope of interpretation of the presented findings. Simply, subjects were treated in a urology clinical setting. This may introduce unintended bias since many of the subjects were seeking medical treatment of various urological conditions. Another potential limitation is that we used total testosterone levels and not free testosterone levels, in combination with signs and symptoms, to evaluate hypogonadism. Additional limitation was that the patients in this registry had different urological complaints and therefore may have different comorbidities.

A major goal of this work was to evaluate long-term results of testosterone treatment, as the maximum duration of any previous study in the literature is 3 years. Generally, diagnosis of hypogonadism allows only for a short period of placebo-controlled design as hypogonadal men are at risk of developing osteoporosis and metabolic diseases. This study was not designed to investigate weight loss, and patients were entered into the registry consecutively once diagnosed with hypogonadism and once they had received at least one year of treatment. This may have implied a bias of some patients dropping out in the early treatment phase due to lack of response.

In our registry, the reason for using T was to treat hypogonadism and ameliorate its symptoms. The impact on weight was neither intended nor expected as weight loss as a result of T treatment had never before been reported in the literature. The profound weight loss of 15.35 kg was in the same magnitude as the 17.23 kg recently reported in a meta-analysis of effects of bariatric surgery (38). In conclusion, T treatment in hypogonadal men for up to 5 years duration appears to be safe and effective in facilitating weight loss, reduction in WC, and reduced BMI.
References


