



Testosterone Deficiency IN MEN

Update on Treatment Strategies



Exclusively for Nurse Practitioners
and Physician Assistants

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Target Audience

Nurse practitioners (NPs) and physician assistants (PAs)
in primary care practice.

Activity Goal


To familiarize NPs and PAs in primary care practices with the lifestyle factors associated with low testosterone levels, to describe the available forms of testosterone replacement therapy (TRT), and to define the goals and potential benefits and risks of TRT.

Learning Objectives

After completing this activity, participants should be better able to:

- Describe the effect of lifestyle interventions on low testosterone levels
- Discuss the benefits and risks of TRT
- List the available forms of TRT
- Develop a treatment regimen, based on the evidence and patient need, to restore proper testosterone levels and alleviate hypogonadal effects

Accreditation Information

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INTRODUCTION

Testosterone deficiency (TD) becomes more common as men age. The estimated prevalence of TD, or hypogonadism, varies widely depending upon the population and the definition of hypogonadism. The commonly cited Baltimore Longitudinal Study of Aging (N = 890) reported a TD prevalence of 12% among men in their 50s and 49% among men in their 80s, using a criterion of total testosterone (TT) level <325 ng/dL (11.3 nmol/L).¹

This activity is provided for 1.0 contact hour under ANCC criteria.

Provided for 1.2 contact hours under Iowa Provider #78. Provider approved by the California Board of Registered Nursing, Provider #13699 for 1.2 contact hours.



This program has been reviewed and is approved for a maximum of 1.0 hour of AAPA Category I CME credit by the Physician Assistant Review Panel. Approval is valid for 1 year from the issue date of November 22, 2010. Participants may submit the self-assessment at any time during that period.

This program was planned in accordance with AAPA's CME Standards for Enduring Material Programs and for Commercial Support of Enduring Material Programs.

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1. Read the newsletter.
2. Relate the content material to the learning objectives.
3. Complete the self-assessment questions and evaluation form online at www.practicingclinicians.com/hypo2. After login, please enter the code: SOPCE71910-2.

Successful completion of the self-assessment is required to earn CME/CE credit. Successful completion is defined as a cumulative score of at least 70%.

The estimated time to complete this activity is 1 hour.

Release date: November 22, 2010

Expiration date: Required materials must be submitted before November 22, 2011

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Mr Herman has nothing to disclose with regard to commercial interests.

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Ms Quallich: *consultant:* Coloplast Group.

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Hypogonadism is defined by both the presence of symptoms and low TT levels.^{2,3} It is associated with sexual symptoms, such as reduced libido and erectile dysfunction; changes in body composition (decreased muscle, increased fat); and decreased bone density.² Observational studies link low testosterone levels to risk of death and to obesity, metabolic syndrome, type 2 diabetes mellitus (T2DM), and atherosclerosis.⁴⁻¹¹

The Endocrine Society recently released updated clinical practice guidelines for use of testosterone replacement therapy (TRT).² The evidence on which the guidelines are based is of less than high quality, based on the subcommittee's own rating system. The guideline does not state a TT threshold at which to consider offering TRT to older men with hypogonadal symptoms.^{2,12}

Lifestyle Interventions and Hypogonadism

Higher body mass index (BMI) is associated with lower TT,^{1,7,9} and obesity has been linked to an elevated prevalence of hypogonadism.⁸ Thus, investigators have studied whether weight loss affects testosterone levels.¹³ In one study, free testosterone and, to a lesser extent, TT, rose significantly during a 9-week rapid weight-loss period

(mean weight loss 16.3 ± 4.5 kg) in 58 men with abdominal obesity and metabolic syndrome. The increase in free testosterone persisted during a 12-month weight-maintenance period, during which subjects maintained most of their weight loss (mean weight loss vs baseline, 14.3 ± 9.1 kg). Much, although not all, of the improvement in TT persisted during the weight-maintenance period (Figure 1). Sex hormone-binding globulin (SHBG) levels increased rapidly during the weight-loss phase but then diminished during the weight-maintenance interval. The proportion of subjects with hypogonadism (TT <317 ng/dL [11 nmol/L] and calculated free testosterone <4.6 ng/dL [160 pmol/L]) decreased from 48% (28/58) at baseline to 9% (5/57) at the end of the weight-loss phase, then rose to 21% (12/58) after completion of the 1-year weight-maintenance period.

These findings substantiate those of a shorter investigation in which TT and SHBG levels increased in response to weight loss (mean 21 kg over 10 weeks) in obese men (mean baseline TT 319.9 ng/dL [11.1 nmol/L] in the treatment group vs 394.8 ng/dL [13.7 nmol/L] in control subjects). The increase in TT was sustained by the end of a 22-week weight-maintenance phase.¹⁴

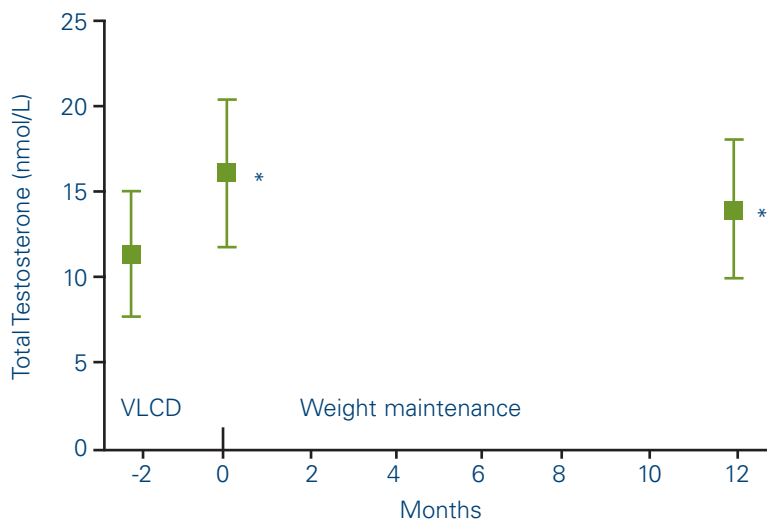


Figure 1. Change in total testosterone (TT) with weight loss in obese men with metabolic syndrome. Mean (SD) levels of TT in 58 middle-aged men with obesity and metabolic syndrome during weight loss and weight maintenance. 48% were hypogonadal at baseline. * $P < .001$ vs baseline. VLCD = very low-calorie diet. Reprinted with permission from Niskanen I, et al.¹³

A recent study evaluated the effect of 1 year of diet and exercise therapy alone compared with diet and exercise plus TRT in 32 hypogonadal men with metabolic syndrome and newly diagnosed T2DM.¹⁵ Diet and exercise therapy alone and diet and exercise plus TRT both led to significant increases in testosterone levels at 1 year. The primary outcome—effect on glycemic control and the metabolic syndrome—is discussed later.¹⁵

Testosterone Replacement Therapy Benefits of TRT

TRT can improve libido, erectile function, body composition (reduced fat mass, increased lean body mass), and bone density.¹⁶⁻²⁰ Some data suggest improved grip strength¹⁹ and mood.^{16,21,22}

T2DM and Metabolic Syndrome

Epidemiologic studies suggest a beneficial effect of TRT on T2DM and metabolic syndrome. Hypogonadism is linked to an elevated prevalence^{8,9} and an elevated risk of diabetes⁶ and metabolic syndrome.⁵ Testosterone levels have been inversely associated with fasting plasma glucose and serum insulin levels.⁷ Some authorities postulate that TD plays a role in the pathology of T2DM and metabolic syndrome and suggest a bidirectional relationship.²³

A small (N = 24), placebo-controlled, crossover study evaluated the effect of TRT for 3 months in hypogonadal men with T2DM who were being treated with either oral hypoglycemic agents or insulin.²⁴ In patients receiving antidiabetic therapy (n = 14), TRT improved glycated hemoglobin (A1C) and increased insulin sensitivity compared with placebo.

In a longer (1-year) recent study, TRT plus diet and exercise but without hypoglycemic medication or insulin therapy resulted in improved glycemic control and regression of metabolic syndrome in hypogonadal men (TT <345.8 ng/dL [12 nmol/L]) with newly diagnosed T2DM.¹⁵ Thirty-two men were randomly assigned to supervised diet and exercise therapy either alone or combined with

Table 1. TRT Formulations

Formulation	Dose	Frequency of Administration	Side Effects Specific to Formulation
Transdermal gel	5-10 g of a 1% testosterone gel applied to shoulders, upper arms, or abdomen ^{27,28}	Daily	Patients should wash hands after applying gel, cover skin with clothing, and wash skin before skin contact to minimize risk of secondary testosterone exposure. ^{27,28} The rate of application-site reactions varies from 2% to 5% depending on product and dosage ^{27,28}
Transdermal patch	One 5-mg, or one 5-mg plus one 2.5-mg, testosterone patch(es) applied over the skin of the back, thigh, or upper arm, avoiding pressure points ²⁹	Every night	Skin reactions at the application site: pruritus, 37%; burnlike blister, 12%; erythema, 7%; vesicles, 6%; burning, 3%; induration, 3% ²⁹
Buccal	One 30-mg bioadhesive tablet applied to buccal mucosa ³⁰	Every 12 hours	Gum or mouth irritation, 9.2%; gum pain, 3.1%; gum tenderness, 3.1%; gum edema, 2%; bitter taste, 4.1%; taste perversion, 2% ³⁰
Subcutaneous pellets	Implanted; dose and regimen vary with the formulation used, patient age, and diagnosis ^{2,31}	Every 3-6 months	Inflammation and pain at site of implantation, ³¹ infection; expulsion of pellet ²
Intramuscular injection	75-100 mg, testosterone enanthate or cypionate weekly or 150-200 mg every 2 weeks ²	Every 1-2 weeks	Associated with supraphysiologic testosterone levels that fall to hypogonadal range by end of dosing interval. Fluctuations in mood, libido; erythrocytosis (especially in older men); cough after injection; pain at injection site ²

TRT. At 1 year, mean (\pm SE) A1C had decreased by $0.5 \pm 0.1\%$ (to $7.1 \pm 0.1\%$) in subjects receiving lifestyle treatment alone and by $1.3 \pm 0.1\%$ (to $6.3 \pm 0.1\%$) in those assigned to lifestyle treatment plus TRT ($P < .001$ between-group difference). All patients receiving TRT reached the A1C goal of $<7\%$ at 1 year compared with 30.4% of those receiving lifestyle therapy alone. More than four-fifths (87.5%) of patients receiving TRT along with diet and exercise therapy attained an A1C $<6.5\%$ at 1 year. Nearly two-thirds (62.5%) of patients treated with TRT along with diet and exercise no longer met the criteria for metabolic syndrome. This was true for only 12.5% of those receiving diet and exercise alone ($P = .003$). Insulin sensitivity also improved significantly more in the TRT group than in the group receiving diet and exercise alone. Diet and exercise ther-

apy alone led to significantly improved glycemic control and amelioration of components of the metabolic syndrome, but adding TRT produced significantly greater benefits ($P < .001$ between groups).¹⁵ This study suggests that testosterone repletion, diet, and exercise may reverse early T2DM in hypogonadal men.

Preliminary results of a larger ($N = 220$), prospective, randomized, double-blind, placebo-controlled trial in hypogonadal men with metabolic syndrome and/or T2DM showed that TRT reduced insulin resistance (homeostatic model of insulin resistance) at 6 months ($P = .018$) in the overall population and at 1 year in subjects with T2DM ($P = .049$). TRT also reduced A1C significantly at 9 months among subjects with T2DM (-0.58% ; $P = .005$), although not at 12 months (0.05% ; $P = .066$).²⁵

Another study revealed no benefit of TRT on insulin secretion or glycemic parameters (fasting or postprandial glycemia) after 2 years of therapy compared with placebo in older men with bioavailable testosterone <103 ng/dL (3.6 nmol/L) and no diabetes at baseline. Some subjects had normal TT levels (median 398 ng/dL [13.8 nmol/L], interquartile range [IQ] 296-465 ng/dL for placebo group [10.3-16.1 nmol/L]; and median TT 371 ng/dL [12.9 nmol/L], IQ 282-465 ng/dL [9.8-16.1 nmol/L] in the TRT group).²⁶

TRT Formulations

TRT may be delivered by transdermal gel or patches, a bioadhesive buccal system, subcutaneous pellet implantation, or intramuscular injection (Table 1). Selection may be based on patient preference, pharmacokinetics, treatment burden, and cost.²

Table 2. Potential Side Effects of TRT

- Erythrocytosis – associated more often with intramuscular formulation^{2,3,32}
- Oily skin, acne^{2,3,33}
- Breast tenderness²
- Diminished sperm production and fertility^{2,32} – use of clomiphene citrate or human chorionic gonadotropin can offset this side effect^{34,35}

Uncommon effects, weak association with TRT²

- Gynecomastia
- Induction or worsening of obstructive sleep apnea
- Male pattern baldness (familial)
- Breast cancer growth

A long-acting undecanoate injectable formulation has been submitted for US Food and Drug Administration approval.

Side Effects of TRT

Side effects associated with TRT are listed in Table 2.

Pretreatment Evaluation

Before initiating TRT, the clinician should assess prostate cancer risk, hematocrit and hemoglobin, voiding symptoms (using International Prostate Symptom score [IPSS]), and sleep apnea history. Patients with a history of low-trauma fracture or osteoporosis should undergo bone density measurement. Table 3 lists absolute and relative contraindications to TRT.²

TRT and Cardiovascular Side Effects in Older Men

Recent studies have evaluated the safety of TRT in older hypogonadal men (aged 65 years and older), especially with regard to cardiovascular events. One randomized, double-blind, placebo-controlled study that focused on this issue was stopped early due to a significantly

higher rate of cardiovascular adverse events in the TRT group compared with the placebo arm (23 vs 5 subjects with cardiovascular events, respectively). About 62% of the 209 subjects enrolled had completed 6 months of therapy when the study was terminated. It is difficult to generalize these data to clinical practice because the study population was frail (eg, had difficulty walking 2 blocks on a level surface or climbing 10 steps) and had a high baseline prevalence of comorbidities and cardiovascular risk factors (eg, hypertension, diabetes, hyperlipidemia, and obesity) as well as being older (mean age, 74 years). Additionally, the study was relatively small. The TRT group also had a higher rate of respiratory and dermatologic events when the trial was discontinued.³⁶

A 6-month-long, randomized, double-blind, placebo-controlled study of TRT in intermediate-frail or frail older men (n = 275; aged 65 years and older) found no change in triglycerides, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) in either group. Hematocrit rose in the TRT group compared with baseline and with the placebo group, but there were no cases of polycythemia. A larger number

of serious adverse events (AEs) occurred in the TRT group (6 vs 3); serious AEs in the TRT group were pulmonary embolism, abdominal aneurysm, heart failure, lung cancer, esophageal cancer, and constrictive pericarditis.¹⁸

A systematic review and meta-analysis of 51 studies evaluating TRT in men without regard to subject age reported no significant effect of TRT on death, cardiovascular, or prostate outcomes. TRT was associated with an increase in hemoglobin and hematocrit, a higher risk of erythrocytosis, and a decrease in HDL-C.³⁷

TRT and Prostate Cancer

Prostate tissue requires androgens to grow,³⁸ and testosterone may stimulate growth of locally advanced and metastatic prostate cancer.³ Thus, a patient's risk of prostate cancer must be assessed before initiating TRT.^{2,3} This involves measuring prostate-specific antigen (PSA); performing a digital rectal examination (DRE); and evaluating risk factors, such as age, family history, race/ethnicity, prior biopsy history, comorbidities, and PSA velocity and density.^{2,3} The Endocrine Society recommends use of the prostate cancer risk calculator, which incorporates most of these factors, to estimate prostate

Table 3. TRT Contraindications

Absolute Contraindications

- Breast cancer
- Metastatic prostate cancer

Relative Contraindications

- Unevaluated prostate nodule or induration
- PSA >3³ or >4 ng/mL² (<3 ng/mL in men at high risk for prostate cancer, eg, African Americans, first-degree relative with prostate cancer) without further urologic evaluation
- Hematocrit >50%² (undergo further clinical evaluation) or >52%³
- Untreated severe obstructive sleep apnea
- Severe lower urinary tract symptoms (IPSS >19² or >21³)
- Uncontrolled or poorly controlled heart failure
- Desire to father children

Bhasin, et al²; Wang, et al.³

cancer risk in men aged 55 to 95 years (<http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp>).^{2,39} However, use of this calculator is not uniformly accepted.^{40,41}

TRT in Men Who Previously Received Treatment for Prostate Cancer

Some clinicians are reluctant to prescribe TRT because of a perception that a higher TT level is associated with an increased risk of prostate cancer.³⁸ Recent analyses do not support this perception. Pooled data from 18 prospective studies in more than 10,000 men (3886 with incident prostate cancer; 6438 controls) revealed no association between risk of prostate cancer and serum testosterone, calculated free testosterone, or most other sex hormones.⁴² Men in these studies were not necessarily hypogonadal.

A retrospective study monitoring PSA changes and prostate cancer incidence in 81 hypogonadal men receiving TRT (mean, 33.8 months; range 6–144 months) concluded that prostate cancer incidence (4/81, 4.9%) was no greater than that of the general population.⁴³ In men who did not have prostate cancer during follow-up, PSA levels did not increase significantly from year to year for 5 years.⁴³ A retrospective review of 57 men who started TRT after radical prostatectomy revealed that PSA did not increase after initiation of TRT. Patients received TRT for an average of 36 months (range 1–136 months) after radical prostatectomy and were followed for an average of 13 months (range 1–99 months) after TRT initiation.⁴⁴ A review of studies of prostate cancer in hypogonadal men receiving TRT found no evidence that TRT raised prostate cancer risk. Prostate cancer incidence in 11 randomized, placebo-controlled studies was similar among hypogonadal men receiving TRT and those receiving placebo (1.2% and 1.5%, respectively).⁴⁵

A retrospective chart review of 96 men receiving high-dose TRT for hypogonadism after management of prostate cancer found that 41 had PSA increases during TRT; 7 had radiographic disease progression. PSA usually declined with

cessation of TRT. About a third of the men (31/96) continued TRT therapy, with no PSA increase or radiologic disease progression after a median of 36.7 months. This subset was distinguished by radical prostatectomy as primary treatment of prostate cancer, low PSA at baseline, and use of dutasteride.⁴⁶

Redefining the Relationship Between Testosterone and Prostate Cancer

Early reports of the association of TT and prostate cancer growth in men with advanced, untreated malignancy were based largely on observations of castrated men.⁴⁷ International guidelines advise that hypogonadal men with a history of definitive treatment for prostate cancer and no residual disease may be considered for TRT.^{3,38} The Endocrine Society guidelines note that “lack of data from randomized trials precludes a general recommendation” regarding use of TRT in men with “organ-confined prostate cancer who have been disease-free for at least 2 years following radical prostatectomy and have undetectable PSA.”² In practice, an increasing number of clinicians are repleting testosterone in symptomatic hypogonadal men who have undergone therapy for localized prostate cancer. Clinicians thereafter follow PSA closely.

Goals of Therapy

The goal of TRT is to ameliorate TD symptoms,² but views differ as to the TT level that therapy should yield.³ An international guideline suggests repleting to the low-normal or mid-normal range for young adult men.^{2,3} Others suggest achieving levels as close to physiologic concentrations as possible.⁴⁸ A recent review suggests that the level required to improve hypogonadism symptoms varies, based in part on genetic polymorphism.⁴⁹ In men receiving testosterone enanthate or testosterone cypionate, The Endocrine Society suggests targeting a TT level of 350 to 750 ng/dL (12–26 nmol/L) at 1 week after injection.²

Libido and sexual function, muscle function, and body composition (reduced

fat, increased muscle) generally improve after 3 to 6 months of TRT.³ BMD takes longer to increase; one study demonstrated significant improvement in spine bone density at 18 and 30 months.^{3,50} If symptoms do not improve within the expected time frame, TRT should be discontinued and the patient evaluated further.³ Symptoms such as low libido and erectile dysfunction may indicate comorbidities or medications rather than TD.³

A chart review of 127 men with TD who initiated TRT over 1 year offers a picture of TRT patients and response in clinical practice. Almost all men presented with erectile dysfunction (22.8%), reduced libido (10.2%), or both (64.6%). Seventy percent showed a symptomatic response to TRT (improved erections, libido, energy, and/or mood) at 3 months,⁵¹ but a slightly smaller proportion (63%) completed 12 months of TRT and a therapeutic response was reported.

Monitoring

Patients receiving TRT should be followed at 1 to 2 months, 3 to 6 months, and then annually. The clinician should evaluate response and adherence to treatment as well as adverse events.^{2,3,32} TT, PSA, and hematocrit or hemoglobin should be measured at 3 to 6 months and then annually.^{2,3} Treatment should be stopped if hematocrit exceeds 54%. If hematocrit later decreases and evaluation reveals no treatment contraindication, TRT may be resumed at a reduced dose.² In men with osteoporosis or a history of low-trauma fracture, The Endocrine Society advises repeating bone mineral density measurement of the lumbar spine, femoral neck, and hip 1 to 2 years after TRT initiation.²

The Endocrine Society suggests PSA surveillance in men aged 40 years and older with a baseline PSA >0.6 ng/mL. After 6 months, it advises following prostate cancer screening guidelines for the man's age and race. The society suggests performing DRE as well as measuring PSA to monitor for prostate cancer, but some authorities disagree with this



CASE: 49-Year-Old Obese Man With Fatigue and Possible Testosterone Deficiency

William is a 49-year-old Caucasian man who presents for a routine physical examination, blood work, and medication refills. At his last visit, he was referred for a sleep study because he complained of fatigue, and that study ruled out obstructive sleep apnea. Today, he complains of worsening fatigue to the point that he cannot complete household chores. William admits that he and his wife rarely have sex and he has little interest in it.

His past medical history includes a diagnosis of both hypertension and dyslipidemia. Also, glucose intolerance has been worsening. He has no surgical history. Screening for depression is negative. He has never been tested for testosterone levels.

Family History

- 76-year-old mother with diabetes, hypertension, and early dementia
- Father died in an automobile accident when William was in college
- Younger brother, aged 48 years, has hypertension and elevated cholesterol levels

Social History

- Lifetime nonsmoker
- Consumes approximately 7 alcoholic beverages a week (mostly red wine)
- Briefly smoked marijuana in college; denies other illicit drug use
- Married; 2 healthy children, both girls
- Works as a high school English teacher
- Exercises by playing golf over the summers when he is off from school

Current Medications

- Lisinopril 20 mg/d
- Simvastatin 40 mg/d

Physical Examination

- Well-developed, obese man
- Height: 5 ft 8 in
- Weight: 198 lb
- BMI: 30.1 kg/m²
- Waist circumference: 41 in
- Vital signs: blood pressure (BP) 132/92 mm Hg, pulse 76 beats/min, respirations 14/min
- DRE: normal findings
- No pathology except for increasing obesity

Laboratory Findings

- Complete blood count: normal without evidence of anemia
- Fasting plasma glucose: 118 mg/dL
- Liver function tests: Normal (hepatitis screen in the past was negative)
- A1C: 6.4%
- Fasting lipids: Total cholesterol, 212 mg/dL; LDL-C, 137 mg/dL; HDL-C, 37 mg/dL; triglycerides, 235 mg/dL; calculated non-HDL-C, 175 mg/dL
- High-sensitivity C-reactive protein: 3.1 mg/dL

recommendation.⁴⁰ A urology consult should be sought if PSA concentration rises by >1.4 ng/mL within any 12-month period during TRT, if DRE reveals a prostatic abnormality, and if the IPSS score >19.²

Summary

TRT can benefit health and quality of life in hypogonadal men by ameliorating symptoms related to libido, sexual function, body composition, and bone density. Emerging evidence suggests that TRT improves glycemic control, insulin sensitivity, and metabolic syndrome in men with diabetes or metabolic syndrome.^{15,24,25} Improved diet and more exercise also increase TT levels.¹³⁻¹⁵ TRT appears to be safe in men with a history of definitive treatment for prostate cancer and no residual disease.^{3,38}

The suboptimal quality of evidence supporting The Endocrine Society recommendations highlights the need for further study of hypogonadism. The quality of evidence on which the society based its recommendations was rated as low or very low. Whether TRT improves diabetes and metabolic syndrome, and evaluation of the threshold at which to consider TRT in older, symptomatic men, requires more research. Data about the risk and benefit of TRT in hypogonadal men are of poorer quality than those addressing use of estrogen and progesterone in postmenopausal women.⁴⁰ An editorial accompanying publication of The Endocrine Society guidelines state, “We could scarcely know less about the long-term effects of testosterone therapy on clinically meaningful outcomes in men.”⁴⁰

PCE Takeaways

- Lifestyle interventions (weight loss, exercise) can add to the beneficial effects of TRT.
- Selection of TRT may be based on patient preferences, pharmacokinetics, treatment burden, and cost.
- The goal of TRT is to ameliorate the symptoms of testosterone deficiency, including sexual symptoms, decreased bone density, and deteriorating body composition.

- Thyroid-stimulating hormone: 2.38 ng/mL
- Vitamin D (25-hydroxyvitamin D): 52 ng/mL
- Total testosterone, 289 ng/dL (normal 40–59 years, 350–890 ng/dL); free testosterone, 6.01 ng/dL; follicle stimulating hormone, luteinizing hormone, and prolactin all within normal range; estradiol, 34 pg/mL (normal, 10–30 pg/mL)
- PSA: 1.1 ng/mL (statistically unchanged from PSA drawn last year)

William meets the criteria for metabolic syndrome. His sedentary lifestyle is likely contributing to his weight gain and perhaps his increasing fatigue and metabolic syndrome. Androgen levels are also sub-optimal, which could be contributing further to his complaints.

William is shocked to learn that he is rapidly approaching frank diabetes. He is advised to improve his diet, concentrating on fresh fruits, vegetables, and low-fat dairy products, and to exercise regularly (at least 45 minutes 5 days a week).

William leaves with 3 prescriptions: lisinopril 40 mg/d (increased from his previous dose of 20 mg/d), simvastatin 80 mg/d (increased from previous dose of 40 mg/d), and TRT (1% 5 g daily) in gel form. He is advised to call in about 4 weeks and to schedule a return visit in 12 weeks. Laboratory work is ordered to be performed 2 weeks before his next visit.

When he returns 3 months later, he reports no side effects from his medications. He has lost 8 lb, is walking with his wife 5 days a week for 30 to 45 minutes, and seems to have “found his energy” for the first time in years. His relationship with his wife has improved, including, he reports, regular intimacy. His BP is now 118/84 mm Hg, and his metabolic profile is improved: Complete blood count and liver function tests remain normal; fasting plasma glucose has decreased to 104 mg/dL; and A1C is 6.0%. Total cholesterol is 189 mg/dL; LDL-C, 113 mg/dL; HDL-C, 42 mg/dL; triglycerides, 165 mg/dL; and calculated

non-HDL-C, 147 mg/dL. High-sensitivity C-reactive protein is 1.9 mg/L, and total testosterone is 415 ng/dL. His DRE is normal. However, William remains overweight (BMI 28.9 kg/m²).

Commentary

William is a middle-aged man with a common presentation—unrelated issues that are all connected: hypertension, dyslipidemia, obesity, fatigue, and sexual dysfunction. His low testosterone level may have contributed to his fatigue, dysmetabolic parameters, and, especially, his low libido. None of these conditions should be treated in a vacuum, and his clinician was wise to take a global approach to treatment. In this case, it produced fairly dramatic results.

Despite his overall improved health profile, William is still overweight. He should be counseled that if he continues to lose weight, he will likely avoid progression to diabetes and may further decrease his BP and improve his cholesterol profile.

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