

## CLINICAL DECISIONS

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## Testosterone-Replacement Therapy

*This interactive feature addresses the approach to a clinical case. A case vignette is followed by specific options, neither of which can be considered correct or incorrect. In short essays, experts in the field then argue for each of the options. Readers can participate in forming community opinion by choosing one of the options and, if they like, providing their reasons.*

## CASE VIGNETTE

Martin is a generally healthy 61-year-old married man who has come to you for his annual physical examination. His medical history is notable only for gastroesophageal reflux disease and mild hyperlipidemia. His current medications include a proton-pump inhibitor and a statin. He stopped smoking years ago and gets most of his exercise from recreational tennis. He reports consuming a glass or two of wine several nights a week. As you discuss Martin's health concerns, he mentions an interest in receiving a prescription for testosterone. He says he's heard a lot recently about low testosterone and even took a quiz on a commercial website. On the basis of his answers to the questions on the quiz — he answered “yes” to questions about decreased energy, decreased ability to play sports, and decreased sexual pleasure and erectile function — the site suggested that he talk to his doctor. Martin adds that he hasn't heard about any downsides to taking testosterone, and he wonders whether it might improve his concentration at work and his noticeably diminishing stamina while playing tennis.

You complete your physical examination and find no abnormalities of the prostate or testes. Martin's blood pressure is 140/75 mm Hg, and his body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) is 31.5. Martin has no symptoms that suggest sleep apnea. In addition to ordering standard laboratory tests, you order a test of the total testosterone level, to be determined from a blood sample obtained early in the morning (before 10 a.m.).

Martin's laboratory results are largely unremarkable, including normal values for fasting

serum glucose, hematocrit, and thyroid function. The lipid profile shows a high-density lipoprotein (HDL) cholesterol level of 45 mg per deciliter (1.2 mmol per liter), a low-density lipoprotein (LDL) cholesterol level of 85 mg per deciliter (2.2 mmol per liter), and a triglyceride level of 120 mg per deciliter (1.35 mmol per liter). Martin's prostate-specific antigen (PSA) level is 3.5, a level that is stable as compared with the level 1 year earlier. Of note, his total serum testosterone level is 275 ng per deciliter (9.53 nmol per liter) (normal range, 300 to 950 ng per deciliter [10.4 to 32.9 nmol per liter]). You ask Martin to repeat the early-morning blood test for testosterone, in accordance with current guidelines; the repeat test shows a total testosterone level of 285 ng per deciliter (9.88 nmol per liter).

## TREATMENT OPTIONS

Which of the following approaches do you think is appropriate for this patient? Base your choice on the published literature, your own experience, recent guidelines, and other sources of information.

1. Recommend testosterone-replacement therapy
2. Recommend against testosterone-replacement therapy

To aid in your decision making, each of these approaches is defended in a short essay by an expert in the field. Given your knowledge of the patient and the points made by the experts, which option would you choose? Make your choice and make recommendations for the patient at NEJM.org.



*Choose an option and comment on your choice at NEJM.org*

## OPTION 1

## Recommend Testosterone-Replacement Therapy

Ronald Swerdloff, M.D.

Martin is a 61-year-old “generally healthy” man who presents for an annual health examination. His BMI places him in the obese category. He is a nonsmoker and plays recreational tennis regularly. His physical examination, including a digital rectal examination, shows no abnormalities. He is taking a statin and has mild hypertriglyceridemia but normal levels of LDL and HDL cholesterol. He asks about testosterone treatment, noting that in his responses to a questionnaire, he reported decreased sexual pleasure and erectile function, as well as decreased energy and performance in sports. He was impressed with marketing informational material that suggested that his testosterone level might be low. His decrease in sexual pleasure, coupled with the other symptoms, was used to justify a decision to test his serum testosterone level.<sup>1</sup>

Two early-morning testosterone levels were obtained, and the results of the two tests (275 and 285 ng per deciliter) were modestly below the reference range (300 to 950 ng per deciliter). Martin’s obesity may have lowered the level of sex hormone-binding globulin (SHBG). Because his serum total testosterone level was only moderately reduced, a free testosterone level should be measured by means of the dialysis method to confirm a diagnosis of hypogonadism. If that level is below the reference range, a presumptive diagnosis of hypogonadism can be made. If the level is within the normal range, further weight-reduction efforts alone may be appropriate.<sup>2</sup> Measuring the levels of serum luteinizing hormone and follicle-stimulating hormone would be helpful to distinguish primary from secondary hypogonadism.<sup>1</sup>

What to do about testosterone therapy? Discuss with Martin the symptoms that are associated with decreased testosterone levels. Advise him that increased body fat, impaired libido, and decreased bone mineral density, muscle mass, and vitality may be seen in men with low serum testosterone but are not specific for the disorder; that high-quality data regarding both benefit and risk of testosterone-replacement

treatment in his age group are limited; and that a low serum testosterone level is associated with increased risks of the metabolic syndrome, type 2 diabetes, and cardiovascular disease.<sup>3</sup> Although recent reports raise the possibility of an increase in cardiovascular risk associated with testosterone-replacement therapy, other data do not show this risk, and the Endocrine Society suggests that a large scale, controlled study is needed to resolve the controversy.<sup>4</sup> Other possible risks, including that of prostate disease,<sup>5</sup> should be discussed with Martin, as advised in the Endocrine Society hypogonadism guidelines. His PSA level has been stable for more than a year, the lower urinary tract symptoms are minimal, and a careful prostate exam was negative. He can be offered a choice between a renewed attempt at weight reduction and testosterone treatment. If Martin states that lifestyle efforts will continue but that his reduction in sexual desire and pleasure is meaningful to him and his spouse, then testosterone-replacement therapy can be initiated, with a target serum testosterone level of 500 ng per deciliter (17.3 nmol per liter) and a 6-month time limit to show a reduction in symptoms.<sup>1</sup> Martin should have regularly scheduled testing for adverse events; a decision on whether to continue treatment can be made at 6 months.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From Harbor UCLA Medical Center, Los Angeles.

## OPTION 2

## Recommend against Testosterone-Replacement Therapy

Bradley D. Anawalt, M.D.

Under a barrage of marketing about low testosterone, men with a broad range of symptoms have inquired about testing and treatment for male hypogonadism.<sup>6</sup> Martin is typical of many such men. He is middle-aged, obese, and relatively sedentary and has a slightly low serum total testosterone level. I recommend against testosterone-replacement therapy for Martin.

Male hypogonadism is defined as symptoms and signs of testosterone deficiency plus low testosterone concentrations as measured in at least two early-morning blood samples.<sup>1</sup> The

symptoms of hypogonadism are myriad and include decreased energy or sense of well-being, but the most useful and specific symptom of male hypogonadism is loss of libido (sexual desire). Weakness, loss of muscle mass, and loss of stamina may also occur with acquired male hypogonadism, but these occur at much lower circulating total testosterone concentrations (less than 150 to 200 ng per deciliter [5.20 to 6.93 nmol per liter]) than those measured in Martin.<sup>7</sup> Although male hypogonadism and erectile dysfunction are often conflated, erectile function is generally preserved until serum total testosterone concentrations are very low.<sup>7</sup>

Obesity is associated with a decrease in serum SHBG, a protein that binds testosterone avidly.<sup>1</sup> Martin, who is obese, probably has low SHBG and normal free (“active”) testosterone concentrations. At worst, Martin has mild testosterone deficiency that is unlikely to cause his symptoms (decreased energy, stamina, sexual pleasure, and erectile function).

What is the danger of missing the diagnosis of male hypogonadism in Martin? In men with hypogonadism, testosterone-replacement therapy has many benefits, including improvement in the sense of well-being and increases in muscle mass and strength, bone density, and libido. However, these effects are directly related to the degree of testosterone deficiency. Increasing Martin’s serum testosterone concentrations to the middle of the normal range for young men is unlikely to benefit him.

The cost, inconvenience, and risks of testosterone-replacement therapy outweigh any potential small benefit for Martin. Transcutaneous testosterone gels, the formulation that is the most frequently prescribed testosterone-replacement therapy in the United States, are expensive and require daily application. The adverse effects of testosterone-replacement therapy for Martin include erythrocytosis and reduced fertility (during treatment).

There is controversy about the potential effects of testosterone-replacement therapy on the risk of prostate cancer and cardiovascular events. On the basis of limited data, this therapy appears not to increase the risk of prostate cancer.<sup>5</sup> However, because Martin’s baseline serum PSA level is at the threshold of the level at which

prostate biopsies are often recommended ( $\geq 4$  mg per deciliter), he is likely to be monitored with serial measurements of serum PSA concentrations. In men with hypogonadism, testosterone-replacement therapy increases serum PSA levels by 0.3 to 0.6 mg per deciliter<sup>2</sup>; receiving this therapy would increase Martin’s likelihood of undergoing invasive testing for prostate cancer. Finally, it is unclear whether testosterone-replacement therapy affects the risk of adverse cardiovascular events,<sup>8</sup> but even a small potential risk is unwarranted when balanced against a small potential benefit.

To address Martin’s symptoms, I would recommend daily exercise (at a more vigorous level than recreational tennis) and reduced caloric intake. If he loses weight, his serum testosterone level might increase. These changes are more likely than “a brew of T” to improve his cardiovascular fitness, sense of well-being, and overall sexual function.

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