REVIEW

THE AMERICAN JOURNAL of MEDICINE®

Testosterone Deficiency

Abdulmaged M. Traish, MBA, PhD,[a,b] Martin M. Miner, MD,[b,c] Abraham Morgentaler, MD,[b,d] Michael Zitzmann, MD[b,e]

[a]Department of Biochemistry and Division of Urology, Boston University School of Medicine, Boston, Mass; [b]The International Society on Men's Health Testosterone Consensus Group; [c]Department of Family Medicine and Urology, Warren Albert School of Medicine, Brown University, Providence, RI; [d]Division of Urology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Mass; [e]Centre for Reproductive Medicine and Andrology/Clinical Andrology Domagkstrasse 11 University Clinics Muenster, Germany

ABSTRACT

Testosterone deficiency (TD) afflicts approximately 30% of men aged 40-79 years, with an increase in prevalence strongly associated with aging and common medical conditions including obesity, diabetes, and hypertension. A strong relationship is noted between TD and metabolic syndrome, although the relationship is not certain to be causal. Repletion of testosterone (T) in T-deficient men with these comorbidities may indeed reverse or delay their progression. While T repletion has been largely thought of in a sexual realm, we discuss its potential role in general men's health concerns: metabolic, body composition, and all-cause mortality through the use of a single clinical vignette. This review examines a host of studies, with practical recommendations for diagnosis of TD and T repletion in middle-aged and older men, including an analysis of treatment modalities and areas of concerns and uncertainty.
 • The American Journal of Medicine (2011) 124, 578-587

KEYWORDS: Cardiovascular disease; Erectile dysfunction; Insulin resistance; Metabolic syndrome; Testosterone

CASE STUDY EXAMPLE

A 52-year-old man of Caucasian descent presented with erectile dysfunction (ED), diminished libido, and fatigue. He took no medications and was otherwise healthy. He was 5 feet, 7 inches tall (170 cm) and weighed 217 pounds (98 kg), with a body mass index of 34 kg/m^2 and a waist circumference of 43 inches (109.2 cm). His blood pressure was 135/80 mm Hg. Laboratory values were all normal except for serum total testosterone of 270 ng/dL (9.37 nmol/L) (normal reference range 300-1000 ng/dL [10.4-34.7 nmol/L]) and fasting serum glucose of 110 mg/dL (6.1mmol/L) (normal 67-99 mg/dL [3.7-5.5mmol/L]), indicating a component of metabolic syndrome (MetS).[1] What are the diagnostic, prognostic, and therapeutic issues in a man with symptomatic testosterone deficiency associated with the metabolic syndrome?

THE CLINICAL PROBLEM

Hypogonadism, henceforth referred to as testosterone deficiency (TD), afflicts approximately 30% of men aged 40-79 years, and its prevalence is associated with aging.[2] The prevalence values differ among the different studies[3-7] due to assessment based on population surveys or clinical settings. Clinical symptoms of TD include fatigue, decreased libido, ED, and negative mood states.[8-11] TD also is associated with changes in body composition, including decreased lean body mass, increased fat mass, and decreased bone mineral density.[8-11] A significant increased risk of TD is noted in association with common medical conditions such as obesity, type 2 diabetes mellitus (T2DM), and hypertension.[8-11] In addition, a strong relationship was observed between TD and the MetS.[12-16] Whereas treatment of TD has been initiated primarily for relief of sexual symptoms, there is now increasing interest among clinicians in addressing the potential adverse metabolic and general health issues associated with TD. Further, recent studies in

Funding: The authors declare that no funds have been received from any pharmaceutical industry for the preparation of this manuscript or any related research funds. Also, we have received no editorial assistance in writing this manuscript. No funds related to this manuscript have been provided by any other organization.

Conflict of Interest: None of the authors have any conflict of interest associated with the work presented in this manuscript.

Authorship: All authors had access to the data and contents of the manuscript, and all authors participated actively in writing, revising, and editing of the manuscript.

Requests for reprints should be addressed to Martin M. Miner, MD, Brown University, Departments of Family Medicine and Urology, Miriam Hospital, Warren Alpert School of Medicine, 164 Summit Avenue, Providence, RI 02906.

E-mail address: martin_miner@brown.edu

0002-9343/$ -see front matter
doi:10.1016/j.amjmed.2010.12.027

women with complete androgen insensitivity syndrome showed increased body fat, abnormal values of cholesterol, and homeostasis model assessment of insulin resistance (HOMA-IR), suggesting that disruption of androgen signaling in women also is associated with metabolic disorders.[17] However, there are limited sources to guide decision-making in commonly seen cases where T replacement therapy (TRT) may be considered, such as in the aforementioned case vignette. It should be noted that African-Americans and Hispanics appear to have a higher risk of developing insulin resistance and type 2 diabetes compared with non-Hispanic whites.[18] Other studies, however, suggested that the number of insulin-sensitive subjects with type 2 diabetes is low and similar among non-Hispanic whites, Hispanics, and African-Americans in the US, and suggested that some ethnic variability exists.[19-22]

CLINICAL SIGNIFICANCE

- Testosterone deficiency is a highly prevalent and under-diagnosed condition associated both with aging and with common medical comorbidities.
- A bidirectional inverse relationship exists between the presence of the number of components of the metabolic syndrome and testosterone levels.
- Testosterone deficiency has a strong association with all-cause mortality and cardiovascular disease risk.
- Early evidence suggests that testosterone replacement therapy may reverse early diabetes mellitus, or improve diabetic control.
- Testosterone replacement therapy is often prescribed to ameliorate sexual signs and symptoms, but may affect improved domains of overall male health.

TD: SIGNS, SYMPTOMS, AND PREVALENCE

Table 1[23,24] lists the signs and symptoms of TD; the most common symptoms are sexual dysfunction (low libido or ED) and chronic fatigue. The prevalence of TD increases with age, ranging from 9% in men in their 50s to 91% of those in their 80s.[25] Mulligan et al[5] found that the rate of TD was ~38.7% in men aged ≥45 years (n = 2165) who visited a primary care provider's office. Although TD is more common among men with certain comorbidities,[5] the decrease in T levels observed with age appears unrelated to illness. Free T fell by about 1.4% per year in men aged 39 to 70 years (n = 1709).[26] Data from the Massachusetts Male Aging Study of approximately 1700 community-dwelling men showed that T levels among men with ≥1 comorbid condition (eg, obesity, cancer, coronary heart disease, hypertension, diabetes, prostate problems) remained 10%-15% lower than those of the control group of subjects, but the rate of decline in free T was similar.[27] In the clinical case presented here, the patient exhibited TD and features of the MetS.[1] The clinical question is whether there is a role for TRT as treatment for the patient's sexual symptoms and MetS.

Table 1 Clinical Manifestations of Testosterone Deficiency

Physical	Psychological	Sexual
Decreased BMD	Depressed mood	Diminished libido
Decreased muscle mass and strength	Diminished energy, sense of vitality, or well-being	Erectile dysfunction
Increased body fat or BMI	Impaired cognition and memory	Difficulty achieving orgasm
Gynecomastia		Decreased morning erections
Anemia		Decreased performance
Frailty		
Fatigue		

BMD = bone mineral density; BMI = body mass index. Adapted from: Petak et al. *Endocr Pract*. 2002;8:440-456[23] and Bhasin et al. *J Clin Endocrinol Metab*. 2006;91:1995-2010.[24]

STRATEGIES AND EVIDENCE

Relationship between TD and MetS and Diabetes

The relationship between TD and MetS is bidirectional, complex, and involves multiple pathophysiological pathways (Figure 1).[6,28-30] Evidence derived from epidemiological and clinical studies[31-51] with TRT in hypogonadal men, as well as androgen deprivation therapy in prostate cancer (PCa) patients, suggests that the link between TD and MetS encompasses multiple pathways, including increased insulin resistance, hyperglycemia, visceral fat accumulation, dyslipidemia, increased inflammatory cytokines, and endothelial dysfunction, leading to vascular disease.[32,34,43-55]

Emerging evidence links TD to multiple cardiovascular risk factors including obesity, diabetes, hypertension, and altered lipid profiles, suggesting that T plays an important role in the regulation of metabolic homeostasis. TD is an independent determinant of endothelial dysfunction,[51-53] thus contributing to vascular pathology. TRT in men with TD produced significant improvement in lipid profiles, reduced body fat and increased lean muscle mass, and decreased fasting glucose levels.[2,11,16,55-57]

TD and All-Cause Mortality and Cardiovascular Disease (CVD) Risk

Epidemiologic studies have identified significant associations between T levels and all-cause and cardiovascular death in general populations of men aged ≥40 years old (Figure 2).[58-60] Mortality rate over a mean of 4.3 years for 858 veterans with normal, equivocal (one normal, one low measurement), and low T levels was 20.1%, 24.6%, and 34.9%, respectively.[58] A larger (2314 men, aged 40-79 years), longer (average 7-year follow-up) nested case-control study found that every 173 ng/dL (6.0 nmol/L) increase

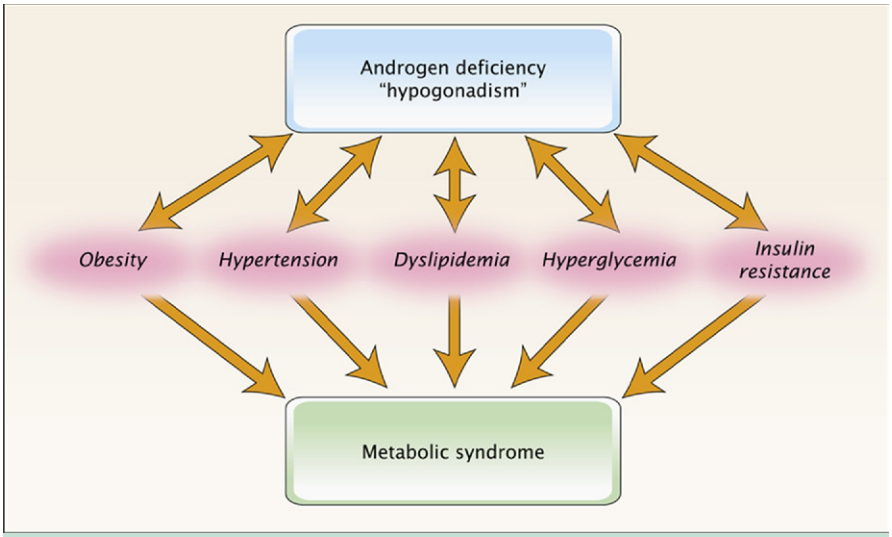

Figure 1 The relationship between testosterone deficiency and metabolic syndrome is bidirectional.[28]

in serum T was associated with a 21% lower risk of all-cause death after excluding deaths within the first 2 years and controlling for multiple variables (age, body mass index, systolic blood pressure, cholesterol, cigarette smoking, diabetes, alcohol intake, physical activity, social class, education, and sex hormone-binding globulin).[59] The Rancho Bernardo study (n = 794 men, aged 50-91 years, average follow-up 11.8 years, but up to 20 years) also found that total and bioavailable T were inversely related to risk of death.[60] Low total T also predicted increased risk of death due to cardiovascular and respiratory disease.[60] Caminiti et al[56] show, in a double-blind, placebo-controlled, randomized trial of 70 elderly patients with chronic heart failure, that long-acting intramuscular T supplementation on top of optimal therapy improves functional exercise capacity, muscle strength, insulin levels, and baroreflex sensitivity.[56] In men at increased risk for cardiovascular events, it may be advisable to obtain cardiology consultation before institution of testosterone therapy.

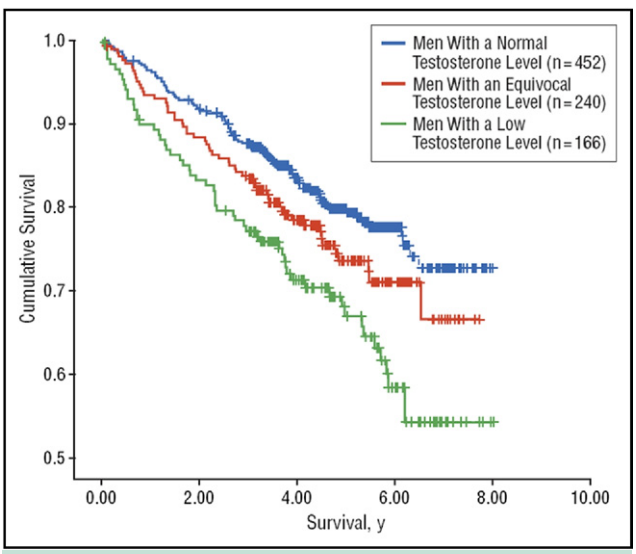

Figure 2 Low testosterone (T) associated with shorter survival. Unadjusted Kaplan-Meier survival curves for 3 T-level groups. Men with low and equivocal (one normal and one low measurement) T levels had a significantly shorter survival than men with normal T levels (log-rank test; $P = .001$). Low testosterone = total T <250 ng/dL (8.7 nmol/L) or free T <.75 ng/dL (.03 nmol/L). Adapted from Shores et al, 2006.[58]

Data from recent randomized placebo-controlled trials of TRT in elderly frail men with limited mobility suggested potential improvements in physical function[33] when T levels were maintained in the physiological range. However, negative cardiovascular risks in older, sicker group men with subclinical vascular disease were noted when T levels were maintained in the higher range.[57] It should be noted that in the latter study, the small sample size, older and sicker population, and mobility limitations precludes the generalizability of these findings. This study raised questions about the use of rather large doses of T in older frail men with subclinical vascular disease.

In contrast to the study by Srinivas-Shankar et al,[33] which showed no serious cardiac adverse events, the Testosterone in Older Men study[57] suffers from serious limitations, these include: patients with subclinical cardiovascular diseases and high prevalence of hypertension, diabetes, hyperlipidemia, and obesity; selection of subjects based on T levels only instead of in combination with clinical symptoms; inadequate randomization; and a dose-seeking study with T doses administered which exceeded those cited in the Endocrine Society Recommendations.[61]

It should be pointed out that monitoring of the adverse events was not the primary end point, and reporting of these events was carried out by telephone interviews of subjects

or reviewing external medical records. Thus, subjective feelings of tachycardia, syncope of unknown origin, arterial hypertension, and myocardial infarctions were all used as cardiovascular adverse events. In fact, in a recent meta-analysis, it was concluded that "the adverse effects of testosterone therapy include an increase in hemoglobin and hematocrit and a small decrease in high-density lipoprotein cholesterol but pointed to no association with cardiovascular events."[62] In addition, several unexplainable observations cast more doubt on the conclusions of this study, including the observation that diabetes and smoking reduced the risk of a cardiac event, and treatment with high T doubled the risk, and normal to high hematocrit increased risk 4- to 5-fold. Despite these unexplained anomalies, the authors drew broad conclusions on the adverse effect of TRT on cardiovascular health in these frail and immobile men. Indeed, the authors stated that "the lack of a consistent pattern in these events and the small number of overall events suggest the possibility that the differences detected between the 2 trial groups may have been due to chance alone."[57]

Can TRT Reverse or Ameliorate MetS or Early Type 2 Diabetes?

MetS is associated with the risk of developing insulin resistance, T2DM, and CVD, and a higher risk of incident CVD and mortality.[63] MetS is associated with a 2-fold increase of 5- to 10-year risk of CVD.[64] Furthermore, the syndrome confers a 5-fold increase in risk for T2DM.[64] Despite this evidence, the clinical use of this category, and in particular its utility as a predictor of CVD, has been the subject of vigorous criticism.[14,15,37,64,65] Accordingly, recent data from a survey involving 880 community-dwelling men supported the construct that MetS is not better than the sum of its components in addressing cardiovascular risk.[66]

The level of evidence supporting TRT in the treatment of MetS, T2DM, and CVD varies because TRT administered in various formulations has differing outcomes on different aspects of clinical end points investigated. Specifically, reduction of body fat, especially intra-abdominal fat, is a key component in treating most individuals with MetS or T2DM, as well as many patients with atherosclerotic cardiovascular disease and dyslipidemia. We consider the evidence supporting TRT in reducing fat mass to be quite rigorous.[67,68] Several randomized clinical trials,[16,69-72] which enrolled 306 patients with MetS, with a mean follow-up of 58 weeks, have been reported. Of those trials, 3 were placebo controlled, whereas 2 open-label trials compared TRT with no treatment. In these trials—enrolling only patients with MetS—TD was defined according to different criteria and TRT was administered in different formulations and doses (Table 2). TRT was associated with a significant reduction of fasting plasma glucose, homeostasis model assessment index (HOMA), triglycerides, and waist circumference. In addition, an increase of high-density lipoprotein cholesterol also was observed, whereas no significant difference was observed for total cholesterol, blood pressure, and body mass index. It should be noted that in the aforementioned studies, some but not all of the patients recruited were receiving statins to reduce cholesterol. The levels of T may be affected by the use of statins because it has been reported that statins and glucose lowering agents use may reduce total but not bioavailable T.[73,74]

Heufelder et al[16] randomized 32 men with TD who were newly diagnosed with T2DM to diet and exercise alone or diet and exercise combined with T gel therapy (50 mg once daily). Subjects had never received insulin or other glucose-lowering therapy, either before or during the trial and had a mean hemoglobin A1C (HbA1C) of 7.5%. At 52 weeks, the group receiving diet and exercise plus T improved significantly on mean serum T concentration, glycemic control (HbA1c), insulin levels and sensitivity, and C-reactive protein levels ($P < .001$ for all between-group comparisons). At study end, serum prostate-specific antigen concentrations were equivalent between groups, an indication of treatment safety.[16]

Value of TRT in TD Patients with ED and Low Libido

Studies of TRT on sexual function and performance vary in quality, although findings are generally consistent. Most studies show that TRT increased sexual awareness and arousal, erectile function, and the frequency of spontaneous erections, but is less consistent in enhancing sexual behavior and performance.[75-85] Overall, the evidence demonstrates that TRT benefits some aspects of sexual desire, erectile function, and performance. This assessment is consistent with a recently published review[86] and meta-analyses of randomized, placebo-controlled trials of TRT in men with sexual dysfunction and varying endogenous T levels.[87] It is worth noting that, because vasculopathy is the most common cause of ED, it also can serve as an early marker for CVD.[88] It is reasonable to obtain T results in men with ED, especially if associated with diminished libido or fatigue, and in men with an inadequate response to phosphodiesterase type-5 inhibitors. T action in these vascular beds may be mediated by several pathways, including vasodilation of blood vessels via activation of K^+ channels or inhibition of Ca^{++} channels.[89,90]

Treatment of TD

A number of TRT preparations are currently available in the US market (Table 2). Intramuscular injections of short-acting T derivatives achieve good serum concentrations within 2-3 days, with levels returning to baseline in most men by 2 weeks, resulting in an injection schedule of 1-2 weeks. Men or their partners may be taught to perform the injection at home. Topical gels or patches provide a more stable serum-T concentration over time than injections. Patches currently available in the US are associated with a high rate of skin reaction, and their use has been largely supplanted by T gels. The main disadvantages of T gels are

Table 2 Testosterone Replacement Therapy Preparations (adapted from Bhasin et al. 2006)[69]

Generic Name (Sample Brands)	Route	Dosing Regimen	Advantages	Disadvantages
T cypionate (Depo-Testosterone) T enanthate (aka ethanate) (Delatestryl), T mixed esters (Sutanon)	IM	200 mg/2 weeks 300 mg/3 weeks 400 mg/4 weeks	Long-acting, relatively inexpensive if self administered; flexibility of dosing.	Requires IM injection, does not mimic physiologic levels, creates peaks and troughs
Injectable long-acting T undecanoate in oil (Nebido)	IM	1000 mg, followed by 1000 mg at 6 wk, and 1000 mg every 12 wks	Infrequent administration	Not approved in the US, IM injection of large volume (4 mL)
Transdermal hydroalcoholic gel (Androgel, Testim)	Topical	5-10 g, delivers 50-100 mg dose daily	Flexible dosing, ease of application, good skin tolerability	Risk of transfer to a female partner or child by skin-to-skin contact if gel not completely dry, moderately high DHT levels
Transdermal T patch (Androderm, Testoderm TTS)	Topical	5 mg/day, applied to skin at bedtime	Mimics physiologic levels and diurnal pattern, ease of application, lesser increase in hemoglobin than injectable esters	Mimics physiologic dosing, contact dermatitis
Scrotal T patch (Testoderm)	Topical	One patch delivers 6 mg over 24 hours, applied daily	Mimics physiologic levels	To promote adherence, scrotal skin needs to be shaved, high DHT levels
Buccal T (Striant)	Gum region	30 mg BID		Gum-related adverse events in 16% of treated men
T pellets (Testopel)	SC	6-12 75-mg pellets implanted SC	Infrequent dosing	Requires surgical incision for insertions, pellets may extrude spontaneously
Oral T undecanoate (Andriol, Androxon, Understor, Restandol, Restinsol)	Oral	40-80 mg 2-3 times/day with meals	Convenience of oral administration	Not approved in the US, variable clinical responses, variable serum T levels, high DHT:T ratio

BID = twice a day; DHT = dihydrotestosterone; IM = intramuscular; SC = subcutaneous.

cost and a black box warning concerning transfer potential to women and children.[91] A long-acting injection formulation (T undecanoate) is dosed every 10-12 weeks, and is available internationally but has not yet been approved for use in the US. T pellets provide 3-6 months of normal serum T, and are placed subcutaneously in the gluteal region via an in-office surgical implantation procedure under local anesthesia; this formulation also has some disadvantages such as extrusion of pellets post surgical procedure.

Diagnosis of TD and TRT to Maintain Threshold Levels

In addition, the genetic background relating to the patient responsiveness to androgens, hence, androgen receptor polymorphisms, are likely to play an inter-individual role.[92] Furthermore, considerable uncertainty exists about 1) the accuracy of T assays, 2) the application of total or free T to clinical assessment of TD, and 3) the subject of age-stratification. Such considerations have to be taken into account when managing patients with TD who definitely need diagnosis and treatment: physicians have to use their clinical judgment and experience in such cases. For a practicing internist, we suggest the following approach to men with symptoms of TD:

Current treatment modalities appear relatively safe, and those adverse events that have been definitively associated with treatment are reversible with cessation of treatment. These include acne, gynecomastia, erythrocytosis, and edema. A number of additional risks have appeared in the literature, but their relationship to TRT is less well established. These include sleep apnea, worsening of urinary voiding symptoms, and prostate cancer. Standard forms of TRT do not appear to adversely affect lipid profiles[55,92,93] or renal function. TRT does not appear to cause liver toxicity, with the exception of oral alkylated T preparations (eg, methyltestosterone), which should not be used for TRT for this reason.

AREAS OF CONCERN AND UNCERTAINTY

Lack of Consensus about Biochemical Identification of Men with TD

A key area of controversy relates to the biochemical determination of TD. There is no defined serum threshold for T

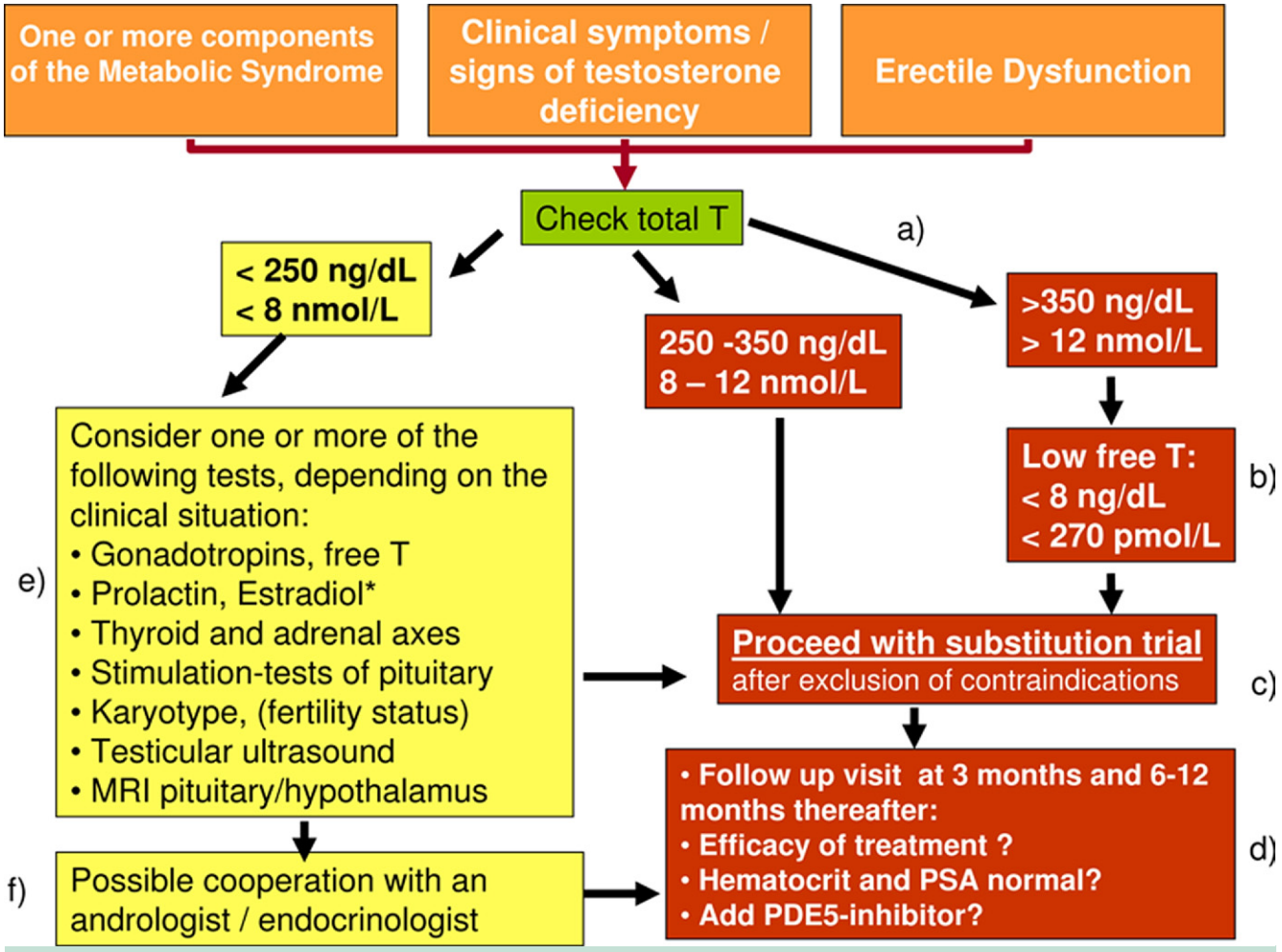

Figure 3 Practical algorithm for work-up and management of testosterone deficiency. Obesity, erectile dysfunction, and the metabolic syndrome are associated with testosterone deficiency, even in men without the characteristic symptoms of diminished libido and fatigue. Although definitive evidence is lacking about the impact of testosterone therapy on metabolic endpoints, we present here an innovative approach based on supportive data regarding surrogate endpoints or early-term results. We believe existing data indicate that a diagnostic work-up is warranted in all of these men. (a) Total testosterone (T) has been the traditional method to diagnose testosterone deficiency. A number of suggested thresholds have been published.[61,105] However, T assays produce highly variable results, and treatment must be individualized based on a combination of clinical presentation and biochemical results. Genetic variation may lead to symptoms of T deficiency in men with normal total T results. (b) Free T can be of diagnostic help in cases where total T does not correspond with clinical presentation. Clinical use of free T is complicated by the availability of a number of assays, and a lack of consensus regarding threshold values. We suggest 8 ng/dL (270 pmol/L) for calculated free T. The analog free T assay[111, 112] shows good correlation with calculated free T, corresponds with biological outcomes, and in our experience has clinical utility, albeit controversial. Values <1.5 ng/dL (52 pmol/L) obtained by the analog free T assay have been suggested as indicating the lower limit of normal. (c) Men with a suspicious prostate examination, or elevated prostate-specific antigen (PSA) should be referred to a urologist for consideration of prostate biopsy before initiation of T therapy. The use of T therapy in men with a prior history of prostate cancer has historically been an absolute contraindication to T therapy. This is an area of active investigation, with recent evidence suggesting the risk is considerably lower than once believed. However, we recommend that the nonspecialist refrain from initiating treatment in such men until there is clearer information as to which men with prior history of prostate cancer may be safely offered T therapy. Contraindications include the presence of elevated hemoglobin or hematocrit at baseline and the desire to initiate a pregnancy within the next 12 months. (d) A symptomatic response to T therapy is generally seen within 3 months. Monitoring should occur at least 2-3 times during the first year, and 1-2 times per year thereafter. Monitoring should include serum T, PSA levels, and hematocrit/hemoglobin. There is no need to measure liver or renal function tests for any of the routine T-therapy formulations. (e) Severe reductions in total T, (ie, <250 ng/dL [8 nmol/L]) are usually accompanied by symptoms or objective measures of T deficiency. Additional diagnostic studies may be indicated depending on the clinical presentation, for example, to exclude the presence of a pituitary mass, or genetic tests. (f) In cases of pituitary disease, genetic causes, unstable glucose control, testicular abnormalities, or the wish for paternity, a specialist should cooperate with the treating physician. PDE-5 = phosphodiesterase type-5.

that clearly distinguishes men who are T deficient from those who are not. Yet all published guidelines recommend one arbitrary threshold or another, generally ranging from 200 to 350 ng/dL (6.94-12.15 nmol/L)]. Variation in sex hormone-binding globulin levels also confounds the interpretation of bioavailable T levels. There is general agreement that free or bioavailable T provides a better estimation of T status, but there is uncertainty about the reliability of those assays. In addition, genetic variation may influence response to circulating T. For these reasons, we believe symptoms of testosterone deficiency, while often not diagnostic or pathognomonic, can play an important role in combination with blood tests in the diagnosis of testosterone deficiency.

A study by Wu et al[94] to identify TD (late-onset hypogonadism) in the general population on the basis of an association between symptoms and levels, examined 3369 men between the ages of 40 and 79 years. The authors found that TD could be identified by presence of 3 sexual symptoms (decreased frequency of morning erection, decreased frequency of sexual thoughts, and erectile dysfunction) combined with a total T of 317 ng/dL(11 nmol/L) and a free T of <220 pmol/L (6.35 pg/mL). Although other nonsexual symptoms may relate to low T levels (physical and psychological) and are present, they do not appear to be a part of the condition of TD (late-onset hypogonadism). This finding in the field of TD is striking. An inverse relationship between an increasing number of sexual symptoms and a decreasing T level was observed. Although the prevalence of hypogonadism is much higher, the prevalence of late-onset hypogonadism is much lower: 2.1%. This underscores the importance of "using not only biochemical measures but also stringently defined, symptom-based criteria to prevent the over-diagnoses of late-onset hypogonadism," as the authors suggest.[94] There are some concerns that this study failed to address, such as increased TD in individuals with comorbidities and metabolic disorders. Thus, defining TD based on purely reduced sexual function alone may not reflect accurately the experience of the clinical realm of the patient.[2-7,95]

Those of us who critically examine the field of TD may not find this study[94] as compelling as the most recent literature that has suggested the potential of T to remedy comorbidities such as MetS and early T2DM. We have sought to take T solely out of the sexual realm and into the metabolic realm and as an overall marker of good health. While this study clearly demonstrates the association of T to sexual symptoms, it does not negate the work of examination of T's impact on metabolic parameters necessary for healthy aging.

TRT and Prostate Cancer (PCa) Risk

The risks associated with TRT are listed in Table 2. An international study identified the greatest concern of physicians with regard to T therapy as potentially stimulating PCa.[96] This concern stems from the use of androgen deprivation for the treatment of advanced prostate cancer. However, current data fail to demonstrate a significant association between serum androgen concentrations and prostate cancer. A large international study comprising 3886 men with PCa and 6438 age-matched controls found no associations between PCa risk and serum concentrations of T, calculated free T, or dihydrotestosterone.[97,98]

A meta-analysis of 19 studies revealed no greater risk of PCa in men diagnosed with TD who received placebo versus men who received T therapy.[99] Although no long-term, large-scale studies on the safety of T therapy have been performed, evidence accumulated over the last 15 years strongly indicates that beyond the near-castrate range there is little, if any impact of changes in serum T on PCa growth.[100]

GUIDELINES

Several guidelines have been published on the investigation, treatment, and monitoring of TD in men.[101-107] The recently published guidelines[61] on management of androgen deficiency revised the recommendations regarding therapy for older men, noted the relationship of TD with concomitant use of long-acting opiates, and added a brief commentary on the use of TRT in men with TD and a history of PCa deemed cured. Perhaps with the advent of these recommendations and the critical examination of the literature published in this field since 2003 and acknowledgement of the gaps of knowledge that continue to exist, this paradigm should be re-examined. It is noteworthy that these guidelines acknowledge that the strength of evidence underlying their recommendations is generally of poor quality, and editorials on this subject also arrived at similar conclusions.[108,109]

CONCLUSIONS AND RECOMMENDATIONS

The patient presented in the clinical vignette is at increased risk for metabolic disorders/T2DM and is likely to die earlier from cardiovascular events than healthier men of his age. The presence of low-serum T concentrations provides an opportunity to treat his symptoms of fatigue and sexual dysfunction, and also to reverse or improve his metabolic status. We therefore recommend a 2- to 3-month trial of TRT, with appropriate monitoring to ensure that adequate serum T levels are achieved. At the end of this period the patient will be assessed for resolution of his symptoms and for physical and biochemical changes, including sexual function, waist circumference, fasting glucose, and lipid profile. Some evidence exists that a 3-month trial showed improvement in several parameters, including energy, mood, and sexual function.[110] Our recommendations here are in general agreement with most published guidelines, with 2 primary sources of disagreement: one is that we emphasize clinical presentation over biochemical thresholds in the diagnosis of TD, and the second is that we believe there is adequate evidence to support the use of TRT in selected cases for metabolic and general health indications (Figure 3).[111,112] It should be noted that while some parameters will be improved during a 3-month trial,[110] anthropomorphic changes are unlikely to change during this short

period. If ED persists, a phosphodiesterase type-5 inhibitor will be prescribed. Diet and exercise recommendations will be encouraged and reinforced.

References

1. Cornier MA, Dabelea D, Hernandez TL, et al. The metabolic syndrome. *Endocr Rev*. 2008;29:777-822.
2. Allan CA, McLachan RI. Age related changes in testosterone and the role of replacement therapy in older men. *Clin Endocrinol.* 2004;60: 653-670.
3. Tajar A, Forti G, O'Neill TW, et al; European Male Aging Study Group. Characteristics of secondary, primary, and compensated hypogonadism in aging men: evidence from the European Male Aging Study. *J Clin Endocrinol Metab.* 2010;95:1810-1818.
4. Wu FC, Tajar A, Pye SR, et al; European Male Aging Study Group. Hypothalamic-pituitary testicular axis disruptions in older men are differentially linked to age and modifiable risk factors: the European Male Aging Study. *J Clin Endocrinol Metab.* 2008;93:2737-2745.
5. Mulligan T, Frick MF, Zuraw QC, Stemhagen A, McWhirter C. Prevalence of hypogonadism in males aged at least 45 years: the HIM study. *Int J Clin Pract*. 2006;60:762-769.
6. Zitzmann M. Testosterone deficiency, insulin resistance and the metabolic syndrome. *Nat Rev Endocrinol.* 2009;5:673-681.
7. Araujo AB, Esche GR, Kupelian V, et al. Prevalence of symptomatic androgen deficiency in men. *J Clin Endocrinol Metab.* 2007;92:4241-4247.
8. Dandona P, Rosenberg MT. A practical guide to male hypogonadism in the primary care setting. *Int J Clin Pract.* 2010;64:682-696.
9. Kaufman JM, Vermeulen A. The decline of androgen levels in elderly men and its clinical and therapeutic implications. *Endocr Rev.* 2005; 26:833-876.
10. Zitzmann M, Faber S, Nieschlag E. Association of specific symptoms and metabolic risks with serum testosterone in older men. *J Clin Endocrinol Metab*. 2006;91:4335-4343.
11. Wang C, Swerdloff RS, Iranmanesh A, et al. Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. *J Clin Endocrinol Metab*. 2000;85:2839-2853.
12. Kupelian V, Page St, Araujo AB, et al. Low sex hormone-binding globulin, total testosterone, and symptomatic androgen deficiency are associated with development of the MetS in non-obese men. *J Clin Endocrinol Metab.* 2006;91:843-850.
13. Laaksonen DE, Niskanen L, Punnonen K, et al. Testosterone and sex hormone-binding globulin predict the metabolic syndrome and diabetes in middle-aged men. *Diabetes Care.* 2004;27:1036-1041.
14. Muller M, Grobbee DE, den Tonkelaar I, Lamberts SWJ, van der Schouw YT. Endogenous sex hormones and metabolic syndrome in aging men. *J Clin Endocrinol Metab*. 2005;90:2618-2623.
15. Laaksonen DE, Niskanen L, Punnonen K, et al. Sex hormones, inflammation and the metabolic syndrome: a population-based study. *Eur J Endocrinol.* 2003;149:601-608.
16. Heufelder AE, Saad F, Bunck MC, Gooren L. Fifty-two-week treatment with diet and exercise plus transdermal testosterone reverses the metabolic syndrome and improves glycemic control in men with newly diagnosed type 2 diabetes and subnormal plasma testosterone. *J Androl.* 2009;30:726-733.
17. Dati E, Baroncelli GI, Mora S, et al. Body composition and metabolic profile in women with complete androgen insensitivity syndrome. *Sex Dev*. 2009;3:188-193.
18. Sumner AE. The relationship of body fat to metabolic disease: influence of sex and ethnicity. *Gend Med.* 2008;5:361-371.
19. Hasson RE, Adam TC, Davis JN, et al. Ethnic differences in insulin action in obese African-American and Latino adolescents. *J Clin Endocrinol Metab*. 2010;95:4048-4051.
20. Haffner SM, Howard G, Mayer E, et al. Insulin sensitivity and acute insulin response in African-Americans, non-Hispanic whites, and Hispanics with NIDDM: the Insulin Resistance Atherosclerosis Study. *Diabetes*. 1997;46:63-69.
21. Karter AJ, Mayer-Davis EJ, Selby JV, et al. Insulin sensitivity and abdominal obesity in African-American, Hispanic, and non-Hispanic white men and women. The Insulin Resistance and Atherosclerosis Study. *Diabetes.* 1996;45:1547-1555.
22. Haffner SM, D'Agostino R, Saad MF, et al. Increased insulin resistance and insulin secretion in nondiabetic African-Americans and Hispanics compared with non-Hispanic whites. The Insulin Resistance Atherosclerosis Study. *Diabetes*. 1996;45:742-748.
23. Petak SM, Nankin HR, Spark RF, Swerdloff RS, Rodriguez-Rigau LJ; American Association of Clinical Endocrinologists. American Association of Clinical Endocrinologists Medical Guidelines for clinical practice for the evaluation and treatment of hypogonadism in adult male patients—2002 update. *Endocr Pract*. 2002;8:440-456.
24. Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in adult men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2006;91:1995-2010.
25. Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. *J Clin Endocrinol Metab*. 2001;86:724-731.
26. Gray A, Feldman HA, McKinlay JB, Longcope C. Age, disease, and changing sex hormone levels in middle-aged men: results of the Massachusetts Male Aging Study. *J Clin Endocrinol Metab*. 1991; 73:1016-1025.
27. Travison TG, Araujo AB, O'Donnell AB, Kupelian V, McKinlay JB. A population-level decline in serum testosterone levels in American men. *J Clin Endocrinol Metab*. 2007;92:196-202.
28. Traish AM, Guay A, Feeley R, Saad F. The dark side of testosterone deficiency: I. Metabolic syndrome and erectile dysfunction. *J Androl*. 2009;30:10-22.
29. Traish AM, Saad F, Guay A. The dark side of testosterone deficiency: II. Type 2 diabetes and insulin resistance. *J Androl*. 2009;30:23-32.
30. Traish AM, Saad F, Feeley RJ, Guay A. The dark side of testosterone deficiency: III. Cardiovascular disease. *J Androl.* 2009;30:477-494.
31. Hak AE, Witteman JCM, de Jong FH, Geerlings MI, Hofman A, Pols HAP. Low levels of endogenous androgens increase the risk of atherosclerosis in elderly men: the Rotterdam Study. *J Clin Endocrinol Metab.* 2002;87:3632-3639.
32. Phillips G, Pinkernell B, Jing T. The association of hypotestosteronemia with coronary artery disease in men. *Arterioscler Thromb* 1994; 14:701-706.
33. Srinivas-Shankar U, Roberts SA, Connolly MJ, et al. Effects of testosterone on muscle strength, physical function, body composition, and quality of life in intermediate-frail and frail elderly men: a randomized, double-blind, placebo-controlled study. *J Clin Endocrinol Metab.* 2010;95:639-650.
34. van Pottelbergh I, Braeckman L, De Bacquer D, De Backer G, Kaufman J. Potential contribution of testosterone and estradiol in the determination of cholesterol and lipoprotein profile in healthy middle-aged men. *Atherosclerosis*. 2003;166:95-102.
35. Makinen JI, Perheentupa A, Irjala K, et al. Endogenous testosterone and serum lipids in middle-aged men. *Atherosclerosis.* 2008;197: 688-693.
36. Makinen J, Jarvisalo M, Pollanen P, et al. Increased carotid atherosclerosis in andropausal middle-aged men. *J Am Coll Cardiol* 2005; 45:1603-1608.
37. Simon D, Charles MA, Nahoul K, et al. Association between plasma testosterone and cardiovascular risk factors in healthy adult men: the Telecom study. *J Clin Endocrinol Metab* 1997;82:682-685.
38. Allan CA, Strauss BJ, Burger HG, Forbes EA, McLachlan RI. Testosterone therapy prevents gain in visceral adipose tissue and loss of skeletal muscle in nonobese aging men. *J Clin Endocrinol Metab*. 2008;93:139-146.
39. Kapoor D, Goodwin E, Channer KS, Jones TH. Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral

adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes. *Eur J Endocrinol*. 2006;154:899-1006.
40. Basaria S, Muller DC, Carducci MA, Egan J, Dobs AS. Hyperglycemia and insulin resistance in men with prostate carcinoma who receive androgen-deprivation therapy. *Cancer.* 2006;106:581-588.
41. Haidar A, Yassin A, Saad F, Shabsigh R. Effects of androgen deprivation on glycaemic control and on cardiovascular biochemical risk factors in men with advanced prostate cancer with diabetes. *Aging Male*. 2007;10:189-196.
42. Yialamas MA, Dwyer AA, Hanley E, Lee H, Pitteloud N, Hayes FJ. Acute sex steroid withdrawal reduces insulin sensitivity in healthy men with idiopathic hypogonadotropic hypogonadism. *J Clin Endocrinol Metab*. 2007;92:4254-4259.
43. Yeap BB, Chubb SA, Hyde Z, et al. Lower serum testosterone is independently associated with insulin resistance in non-diabetic older men: the Health in Men Study. *Eur J Endocrinol*. 2009;161:591-598.
44. Stellato RK, Feldman HA, Hamdy O, Horton ES, McKinlay JB. Testosterone, sex hormone-binding globulin, and the development of type 2 diabetes in middle-aged men: prospective results from the Massachusetts male aging study. *Diabetes Care.* 2000;23:490-494.
45. Selvin E, Feinleib M, Zhang L, et al. Androgens and diabetes in men. *Diabetes Care.* 2007;30:234-238.
46. Pitteloud N, Hardin M, Dwyer AA, et al. Increasing insulin resistance is associated with a decrease in Leydig cell testosterone secretion in men. *J Clin Endocrinol Metab*. 2005;90:2636-2641.
47. Pitteloud N, Mootha VK, Dwyer AA, et al. Relationship between testosterone levels, insulin sensitivity, and mitochondrial function in men. *Diabetes Care*. 2005;28:1636-1642.
48. Oh JY, Barrett-Connor E, Wedick NM, Wingard DL; Rancho Bernardo Study. Endogenous sex hormones and the development of type 2 diabetes in older men and women; the Rancho Bernardo study. *Diabetes Care*. 2002;25:55-60.
49. Traish AM, Feeley RJ, Guay A. Mechanisms of obesity and related pathologies: androgen deficiency and endothelial dysfunction may be the link between obesity and erectile dysfunction. *FEBS J*. 2009;276: 5755-5767.
50. Fukui M, Kitagawa Y, Ose H, Hasegawa G, Yoshikawa T, Nakamura N. Role of endogenous androgen against insulin resistance and athero- sclerosis in men with type 2 diabetes. *Curr Diabetes Rev*. 2007;3:25-31.
51. Akishita M, Hashimoto M, Ohike Y, et al. Low testosterone level is an independent determinant of endothelial dysfunction in men. *Hypertens Res.* 2007;30:1029-1034.
52. Akishita M, Hashimoto M, Ohike Y, et al. Low testosterone level as a predictor of cardiovascular events in Japanese men with coronary risk factors. *Atherosclerosis.* 2009;210:232-236.
53. Malkin CJ, Pugh PJ, Jones RD, Kapoor D, Channer KS, Jones TH. The effect of testosterone replacement on endogenous inflammatory cytokines and lipid profiles in hypogonadal men. *J Clin Endocrinol Metab*. 2004;89:3313-3318.
54. Nettleship JE, Pugh PJ, Channer KS, Jones T, Jones RD. Inverse relationship between serum levels of interleukin-1beta and testosterone in men with stable coronary artery disease. *Horm Metab Res*. 2007;39:366-371.
55. Traish AM, Abdou R, Kypreos KE. Androgen deficiency and atherosclerosis: the lipid link. *Vascul Pharmacol.* 2009;51:303-313.
56. Caminiti G, Volterrani M, Iellamo F, et al. Effect of long-acting testosterone treatment on functional exercise capacity, skeletal muscle performance, insulin resistance, and baroreflex sensitivity in elderly patients with chronic heart failure a double-blind, placebo-controlled, randomized study. *J Am Coll Cardiol*. 2009;54:919-927.
57. Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. *N Engl J Med*. 2010;363:109-122.
58. Shores MM, Matsumoto AM, Sloan KL, Kivlahan DR. Low serum testosterone and mortality in male veterans. *Arch Intern Med*. 2006; 166:1660-1665.
59. Khaw K-T, Dowsett M, Folkerd E, et al. Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men: European Prospective Investigation Into Cancer in Norfolk (EPIC-Norfolk) Prospective Population Study. *Circulation.* 2007; 116:2694-2701.
60. Laughlin GA, Barrett-Connor E, Bergstrom J. Low serum testosterone and mortality in older men. *J Clin Endocrinol Metab.* 2008;93: 68-75.
61. Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2010;95:2536-2559.
62. Fernández-Balsells MM, Murad MH, Lane M, et al. Clinical review 1: adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2010;95:2560-2575.
63. Lorenzo C, Williams K, Hunt KJ, Haffner SM. The National Cholesterol Education program—Adult Treatment Panel III, International Diabetes Federation, and World Health Organization definitions of the metabolic syndrome as predictors of incident cardiovascular disease and diabetes. *Diabetes Care*. 2007;30:8-13.
64. Esposito K, Giugliano F, Martedi E, et al. High proportions of erectile dysfunction in men with metabolic syndrome. *Diabetes Care*. 2005; 28:1201-1203.
65. Osuna JA, Gómez-Pérez R, Arata-Bellabarba G, Villaroel V. Relationship between BMI, total testosterone, sex hormone-binding-globulin, leptin, insulin and insulin resistance in obese men. *Arch Androl*. 2006;52:355-361.
66. Guembe MJ, Toledo E, Barba J, et al. Association between metabolic syndrome or its components and asymptomatic cardiovascular disease in the RIVANA-study. *Atherosclerosis*. 2010;211:612-617.
67. Hobbs CJ, Plymate SR, Rosen CJ, Adler RA. Testosterone administration increases insulin-like growth factor-I levels in normal men. *J Clin Endocrinol Metab.* 1993;77:776-779.
68. Singh R, Artaza JN, Taylor WE, et al. Testosterone inhibits adipogenic differentiation in 3T3-L1 cells: nuclear translocation of androgen receptor complex with beta-catenin and T-cell factor 4 may bypass canonical Wnt signaling to down-regulate adipogenic transcription factors. *Endocrinology*. 2006;147:141-154.
69. Kalinchenko SY, Tishova YA, Mskhalaya GJ, Gooren LJ, Giltay EJ, Saad F. Effects of testosterone supplementation on markers of the metabolic syndrome and inflammation in hypogonadal men with the metabolic syndrome: the double-blinded placebo-controlled Moscow study. *Clin Endocrinol (Oxf)*. 2010;73: 602-612.
70. Aversa A, Bruzziches R, Francomano D, Spera G. Efficacy and safety of two different testosterone undecanoate formulations in hypogonadal men with metabolic syndrome. *J Endocrinol Invest.* 2010;33: 776-783.
71. Aversa A, Bruzziches R, Francomano D, Rosano G, Lenzi A, Spera G. Effects of testosterone undecanoate on cardiovascular risk factors and atherosclerosis in middle-aged men with late onset hypogonadism and metabolic syndrome: results from a 24-months, randomized double blind placebo-controlled study. *J Sex Med* 2010;7:3495-3503.
72. La Vignera S, Calogero AE, D'Agata R, et al. Testosterone therapy improves the clinical response to conventional treatment for male patients with metabolic syndrome associated to late onset hypogonadism. *Minerva Endocrinol*. 2008;33:159-167.
73. Stanworth RD, Kapoor D, Channer KS, Jones TH. Statin therapy is associated with lower total but not bioavailable or free testosterone in men with type 2 diabetes. *Diabetes Care*. 2009;32:541-546.
74. Kapoor D, Channer KS, Jones TH. Rosiglitazone increases bioactive testosterone and reduces waist circumference in hypogonadal men with type 2 diabetes. *Diab Vasc Dis Res.* 2008;5(2):135-137.
75. Corona G, Maggi M. The role of testosterone in erectile dysfunction. *Nat Rev Urol*. 2010;7:46-56.
76. Svartberg J, Aasebo U, Hjalmarsen A, Sundsfjord J, Jorde R. Testosterone treatment improves body composition and sexual function in men with COPD, in a 6-month randomized controlled trial. *Resp Med*. 2004;98:906-913.

77. Anderson RA, Bancroft J, Wu FC. The effects of exogenous testosterone on sexuality and mood of normal men. *J Clin Endocrinol Metab.* 1992;75:1503-1507.
78. Aversa A, Isidori AM, Spera G, Lenzi A, Fabbri A. Androgens improve cavernous vasodilation and response to sildenafil in patients with erectile dysfunction. *Clin Endocrinol.* 2003;58:632-638.
79. Benkert O, Witt W, Adam W, Leitz A. Effects of testosterone undecanoate on sexual potency and the hypothalamic-pituitary-gonadal axis of impotent males. *Arch Sex Behav.* 1979;8:471-479.
80. Cavallini G, Caracciolo S, Vitali G, Modenini F, Biagiotti G. Carnitine versus androgen administration in the treatment of sexual dysfunction, depressed mood, and fatigue associated with male aging. *Urology.* 2004;63:641-646.
81. Kunelius P, Lukkarinen O, Hannuksela ML, Itkonen O, Tapanainen JS. The effects of transdermal dihydrotestosterone in the aging male: a prospective, randomized, double blind study. *J Clin Endocrinol Metab.* 2002;87:1467-1472.
82. Park NC, Yan BQ, Chung JM, Lee KM. Oral testosterone undecanoate (Andriol) supplement therapy improves the quality of life for men with testosterone deficiency. *Aging Male*. 2003;6:86-93.
83. Schiavi RC, White D, Mandeli J, Levine AC. Effect of testosterone administration on sexual behavior and mood in men with erectile dysfunction. *Arch Sex Behav.* 1997;26:231-241.
84. Shabsigh R, Kaufman JM, Steidle C, Padma-Nathan H. Randomized study of testosterone gel as adjunctive therapy to sildenafil in hypogonadal men with erectile dysfunction who do not respond to sildenafil alone. *J Urol*. 2004;172:658-663.
85. Shabsigh R. Testosterone therapy in erectile dysfunction and hypogonadism. *J Sex Med.* 2005;2:785-792.
86. Bolona ER, Uraga MV, Haddad RM, et al. Testosterone use in men with sexual dysfunction: a systematic review and meta-analysis of randomized placebo-controlled trials. *Mayo Clin Proc*. 2007;82(1):20-28.
87. Isidori AM, Giannetta E, Gianfrilli D, et al. Effects of testosterone on sexual function in men: results of a meta-analysis. *Clin Endocrinol (Oxf)*. 2005;63:381-394.
88. Miner MM, Kuritzky L. Erectile dysfunction: a sentinel marker for cardiovascular disease in primary care. *Cleve Clin J Med*. 2007; 74(Suppl 3):S30-S37.
89. Yildiz O, Seyrek M. Vasodilating mechanisms of testosterone. *Exp Clin Endocrinol Diabetes.* 2007;115:1-6.
90. Seyrek M, Yildiz O, Ulusoy HB, Yildirim V. Testosterone relaxes isolated human radial artery by potassium channel opening action. *J Pharmacol Sci.* 2007;103:309-316.
91. Lakshman KM, Basaria S. Safety and efficacy of testosterone gel in the treatment of male hypogonadism. *Clin Interv Aging*. 2009;4:397-412.
92. Zitzmann M, Nieschlag E. Androgen receptor gene CAG repeat length and body mass index modulate the safety of long-term intramuscular testosterone undecanoate therapy in hypogonadal men. *J Clin Endocrinol Metab.* 2007;92:3844-3853.
93. Saad F, Gooren LJ, Haider A, Yassin A. A dose-response study of testosterone on sexual dysfunction and features of the metabolic syndrome using testosterone gel and parenteral testosterone undecanoate. *J Androl.* 2008;29:102-105.
94. Wu FCW, Tajar A, Beynon J, et al. Identification of late-onset hypogonadism in middle-aged and elderly men. *N Engl J Med.* 2010;363:123-135.
95. Zitzmann M. Testosterone deficiency and treatment in older men: definition, treatment, pitfalls. *Asian J Androl.* 2010;12:623-625.
96. Gooren LJ, Behre HM, Saad F, Frank A, Schwerdt S. Diagnosing and treating testosterone deficiency in different parts of the world. Results from global market research. *Aging Male*. 2007;10:173-181.
97. Endogenous Hormones and Prostate Cancer Collaborative Group. Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. *J Natl Cancer Inst.* 2008;100:170-183.
98. Carpenter WR, Whitney RR, Godley PA. Getting over testosterone: postulating a fresh start for etiologic studies of prostate cancer [Editorial]. *J Natl Cancer Inst.* 2008;100:158-159.
99. Calof OM, Singh AB, Lee ML, et al. Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials. *J Gerontol A Biol Sci Med Sci.* 2005;60:1451-1457.
100. Morgentaler A, Traish AM. Shifting the paradigm of testosterone and prostate cancer: the saturation model and the limits of androgen-dependent growth. *Eur Urol.* 2009;55:310-320.
101. Wang C, Nieschlag E, Swerdloff RS, et al. ISA, ISSAM, EAU, EAA and ASA recommendations: investigation, treatment and monitoring of late-onset hypogonadism in males. *Aging Male.* 2009;12:5-12.
102. Nieschlag E, Swerdloff R, Behre HM, et al.; International Society of Andrology (ISA); International Society for the Study of the Aging Male (ISSAM); European Association of Urology (EAU). Investigation, treatment and monitoring of late-onset hypogonadism in males. ISA, ISSAM, and EAU recommendations. *Eur Urol*. 2005;48:1-4.
103. Nieschlag E, Swerdloff R, Behre HM, et al. Investigation, treatment and monitoring of late-onset hypogonadism in males. *Aging Male*. 2005;8:56-58.
104. Nieschlag E, Swerdloff R, Behre HM, et al. Investigation, treatment and monitoring of late-onset hypogonadism in males: ISA, ISSAM, and EAU recommendations. *Int J Androl.* 2005;28:125-127.
105. Wang C, Nieschlag E, Swerdloff R, et al. Investigation, treatment, and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA, and ASA recommendations. *J Androl*. 2009;30:1-9.
106. Wang C, Nieschlag E, Swerdloff R, et al. ISA, ISSAM, EAU, EAA and ASA recommendations: investigation, treatment and monitoring of late-onset hypogonadism in males. *Int J Impot Res.* 2009;21:1-8.
107. Kazi M, Geraci SA, Koch CA. Considerations for the diagnosis and treatment of testosterone deficiency in elderly men. *Am J Med*. 2007;120:835-840.
108. Anawalt BD. Guidelines for testosterone therapy for men: how to avoid a mad (t)ea party by getting personal. *J Clin Endocrinol Metab.* 2010;95:2614-2617.
109. McLachlan RI. Certainly more guidelines than rules. *J Clin Endocrinol Metab*. 2010;95:2610-2613.
110. Jockenhövel F, Minnemann T, Schubert M, et al. Timetable of effects of testosterone administration to hypogonadal men on variables of sex and mood. *Aging Male*. 2009;12:113-118.
111. Morgentaler A. Commentary: guideline for male testosterone therapy: a clinician's perspective. *J Clin Endocrinol Metab.* 2007;92: 416-417.
112. Moreno S, Shyam A, Morgentaler A. Comparison of free testosterone results by analog radioimmunoassay and calculated free testosterone in an ambulatory clinical population. *J Sex Med.* 2010;7:1948-1953.