MAYO CLINIC

Adult-Onset Hypogonadism

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Abstract

In August 2015, an expert colloquium commissioned by the Sexual Medicine Society of North America (SMSNA) convened in Washington, DC, to discuss the common clinical scenario of men who present with low testosterone (T) and associated signs and symptoms accompanied by low or normal gonadotropin levels. This syndrome is not classical primary (testicular failure) or secondary (pituitary or hypothalamic failure) hypogonadism because it may have elements of both presentations. The panel designated this syndrome adult-onset hypogonadism (AOH) because it occurs commonly in middle-age and older men. The SMSNA is a not-for-profit society established in 1994 to promote, encourage, and support the highest standards of practice, research, education, and ethics in the study of human sexual function and dysfunction. The panel consisted of 17 experts in men's health, sexual medicine, urology, endocrinology, and methodology. Participants declared potential conflicts of interest and were SMSNA members and nonmembers. The panel deliberated regarding a diagnostic process to document signs and symptoms of AOH, the rationale for T therapy, and a monitoring protocol for T-treated patients. The evaluation and management of hypogonadal syndromes have been addressed in recent publications (ie, the Endocrine Society, the American Urological Association, and the International Society for Sexual Medicine). The primary purpose of this document was to support health care professionals in the development of a deeper understanding of AOH, particularly in how it differs from classical primary and secondary hypogonadism, and to provide a conceptual framework to guide its diagnosis, treatment, and follow-up.

 ■ Mayo Clin Proc. 2016;91(7):908-926

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The Sexual Medicine Society of North America defines *adult-onset hypogonadism* (AOH) as a clinical and biochemical syndrome characterized by a deficiency of testosterone (T) with symptoms and signs that can be caused by testicular and/or hypothalamic-pituitary (HP) dysfunction; *AOH is therefore clinically distinct from classical primary and secondary hypogonadism*. This syndrome is characterized by T deficiency and the failure to mount an adequate compensatory pituitary response to low T levels; gonadotropin levels are low or in the normal range.

Hypogonadism is classically defined as primary or secondary. Primary hypogonadism (hypergonadotrophic hypogonadism) is the result of testicular failure to produce adequate levels of T, and is identified by low T and elevated gonadotropin levels (luteinizing hormone [LH]; follicle-stimulating hormone [FSH]). Secondary hypogonadism (hypogonadotrophic hypogonadism) is the result of gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency (eg, pituitary or hypothalamic failure), which may be congenital or may arise from various pathological processes including HP injury from tumors, trauma, or radiation.

In March 2015, the Food and Drug Administration issued a drug safety communication cautioning about the use of T products for low T levels as a result of aging and required US manufacturers of prescription T products to amend drug labels to include

warnings of possible increased risk of heart attack and stroke. Prescribing information was amended to indicate that T is appropriate for replacement only in adult men with low T levels because of damage or trauma to the testes (ie, orchitis, Klinefelter syndrome, etc), because of gonadotropin or LHRH deficiency, or because of damage to the pituitary or the hypothalamus. Testosterone treatment was not recommended for men who do not fall into these categories (ie, men with AOH).

These classical definitions of hypogonadism that are based on specifying a testicular or a pituitary-hypothalamic site of failure may not apply to a large portion of hypogonadal men assessed in population-based studies and seen in clinical practice. In many men, low T levels are accompanied by normal or low levels of gonadotropins—a presentation that may arise from failure at both the testicular and pituitary-hypothalamic levels; this possibility is not captured by the primary vs secondary hypogonadism dichotomy. Several medical societies have grappled with this issue and proposed revised terminology to clarify the identification, categorization, diagnosis, and treatment of hypogonadal men and, in particular, the concern that the primary vs secondary distinction does not adequately or accurately define men with AOH (eg, the Endocrine Society,[1] the American Urological Association,[2] and the International Society for Sexual Medicine[3]).

The panel approached this issue by examining data from epidemiological and large clinical studies. Adult-onset hypogonadism is well illustrated by an examination of hypogonadal men in the European Male Ageing Study (EMAS).[4] Four groups were defined on the basis of normal cutoff values of 10.5 nmol/L (300 ng/dL) for total T and 9.4 U/L for LH among 3369 community-dwelling men aged 40 to 79 years in 8 European cities (see Figure 1). On the basis of these thresholds, it was found that approximately 2.0% of men had primary hypogonadism (low T, high LH), 9.5% of men had "compensated" hypogonadism (normal T, high LH), and 11.8% of men were classified as having secondary hypogonadism with low T accompanied by low or normal LH, a presentation consistent with AOH.

Pathophysiology

The classical framework for the diagnosis of hypogonadism uses the anatomic approach that is shared with other endocrine disorders. Primary testicular disorders impair both Leydig and seminiferous tubule function, resulting in reduced T synthesis and hypospermatogenesis. The etiologies include XXY karyotype (Klinefelter syndrome), toxicities (chemotherapy-induced), infectious destruction (mumps orchitis), or radiation-induced damage. The hormonal pattern is a low serum T level with elevated serum gonadotropin levels. Secondary hypogonadism, also called centrally mediated hypogonadism, is classically due to destruction or infiltration of the pituitary gland, resulting in reduced gonadotropin synthesis and low circulating T level. Etiologies include pituitary tumors (secretory or nonsecretory), granulomatous invasion, or infectious complications. Some patients have congenital or acquired disorders resulting in LHRH (gonadotropin-releasing hormone [GnRH]) deficiency.

Many chronic illnesses are associated with low T levels but do not fit into the 2 classical endocrine situations described above. These syndromes, with clinical symptoms of hypogonadism, are acquired in adulthood and often exhibit functional hyposecretion at the level of both pituitary and testis.

Prevalence of AOH

One of the challenges of diagnosing and treating AOH is that its true prevalence is unclear. Epidemiological studies vary in how androgen deficiency (AD) was defined and in whether signs and symptoms were considered. In addition, even when men are categorized as having primary vs secondary hypogonadism, the designation of secondary hypogonadism does not establish the extent to which the low T level is truly the consequence of inadequate gonadotropins—some of these men may well have a primary testicular failure component. The breakdown of the primary vs secondary distinction highlights the need for a more accurate definition of these patients (eg, AOH). These studies provide useful information, however, given that AOH is conceptualized as a subgroup of men with signs and symptoms who have an inadequate pituitary response to low T levels.

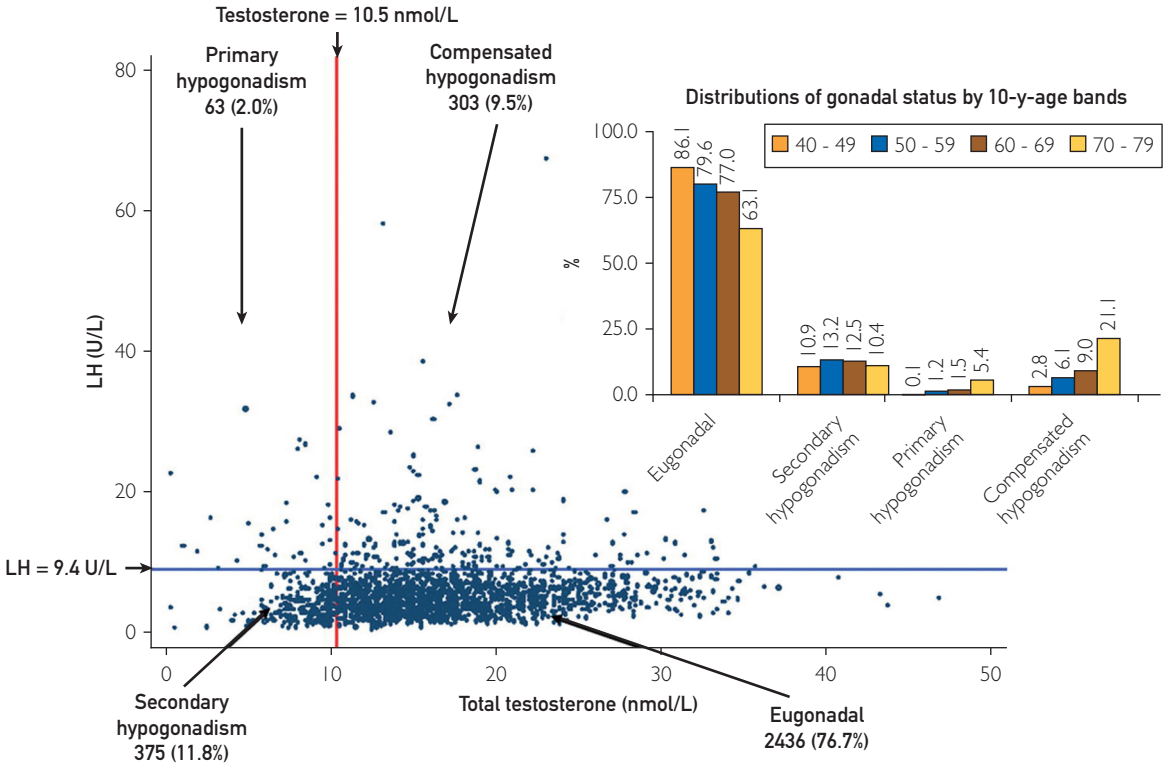

FIGURE 1. Subgroups of men by gonadal status and by decade of age from the European Male Ageing Study (EMAS).[4] LH = luteinizing hormone. From *J Clin Endocrinol Metab*,[4] with permission.

In the EMAS, the prevalence of hypogonadism was 13.8%; of these men, 85.5% were classified as having secondary hypogonadism.[4] The prevalence of hypogonadism in a group of 990 men seeking care for sexual dysfunction was 36% (359); of these men, 83.8% (301 out of 359) had secondary hypogonadism.[5] Similarly, 87.1% (727/835) of men with hypogonadism were classified as having secondary hypogonadism by Maseroli et al[6] when reporting on a large series of patients presenting at an emergency department clinic (n=3847). Another report on an overlapping cohort from the same clinic noted that approximately 87.5% (724/827) of men with hypogonadism had secondary hypogonadism.[7]

Importantly, among men with secondary hypogonadism, only 11% had a specific medical condition (eg, genetics, surgery, radiotherapy, and trauma) that could account for the hypogonadism; the etiology in the remaining 89% was unknown[8] (see Figure 2). The term AOH could be applied to the overwhelming majority of these men, many of whom also had concomitant metabolic disease (ie, obesity, type 2 diabetes [DM2], or metabolic syndrome [MetS]; see Figure 3). It is noteworthy that Camacho et al[9] reported that weight gain and obesity are significantly associated with low total T and low free T levels.

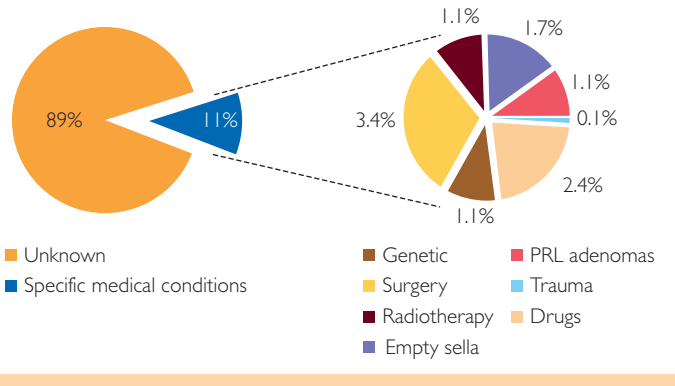

FIGURE 2. In a group of 4220 men presenting to a sexual dysfunction clinic, only 11% of those diagnosed with secondary hypogonadism had a diagnosable medical cause for the condition.[8] PRL = prolactin.

Mayo Clin Proc. ■ July 2016;91(7):908-926 ■ http://dx.doi.org/10.1016/j.mayocp.2016.04.022
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When symptoms are part of the hypogonadism definition, the prevalence is lower. The Boston Area Community Health (BACH) Survey assessed symptomatic AD in a population of 1475 randomly selected men aged 30 to 79 years.[10] Approximately 5.6% of men met criteria for symptomatic AD, which was defined as low total or free T levels in addition to having low libido, erectile dysfunction, osteoporosis or fracture, or having 2 or more of the following symptoms: sleep disturbance, depressed mood, lethargy, or diminished physical performance. In the EMAS, 2.1% of men had symptomatic late-onset hypogonadism (LOH), defined as low total and free T levels with at least 3 sexual symptoms.[11]

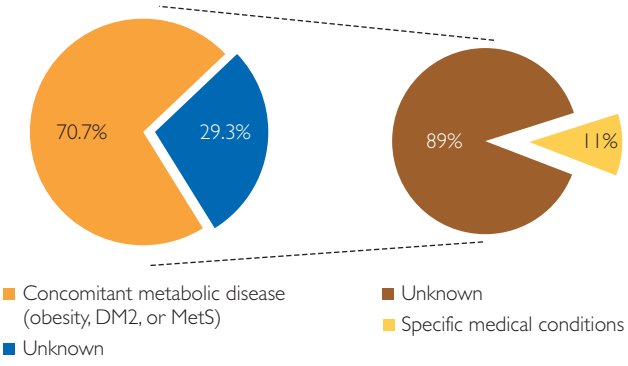

FIGURE 3. Medical conditions associated with secondary hypogonadism in a sample of 4220 men presenting to a sexual dysfunction clinic; 89% of men diagnosed with secondary hypogonadism did not have a diagnosable source for the condition. Most of these patients (70.7%) had a concomitant metabolic disease.[8] DM2 = type 2 diabetes; MetS = metabolic syndrome.

The Influence of Aging

The relationship between aging and hypogonadism is complex. Among healthy aging men, hypothalamic-pituitary-gonadal (HPG) function may be maintained.[12-14] In a broader population of men, many of whom have comorbidities, hypogonadism prevalence may increase with age (eg, the Baltimore Longitudinal Study of Aging).[15] The prevalence may be higher among men 65 years or older although prevalence rates by decade up to age 84 years have been reported as statistically indistinguishable (range, 34%-45.5%).[16] When symptoms are considered, similar patterns emerge. In the longitudinal Massachusetts Male Aging Study, symptomatic AD prevalence at baseline was similar for men aged 40 to 49 years (4.1%) and 50 to 59 years (4.5%) but was increased among men aged 60 to 70 years (9.4%).[17] A similar pattern was reported for men in the BACH study.[10] Prevalence rates of symptomatic AD by decade among men aged 30 to 69 years ranged from 3.1% to 7.0% and were statistically indistinguishable; the prevalence rate for men aged 70 to 79 years, however, was 18.1%.

Adult-onset hypogonadism, unlike overall hypogonadism, may be less influenced by age. In the EMAS, the prevalence of primary hypogonadism in men increased significantly with age but among men with low T and normal LH levels—men likely to have AOH—age was not a significant predictor.[4]

Although healthy aging men appear to maintain HPG function, evidence from broader populations indicates that beginning at age 20 to 30 years, T levels decline by 0.3% to 1.4% per year.[18] It is believed that declining T levels are partly the result of primary testis failure—the Leydig cells become less responsive to exogenous gonadotropin stimulation[19] and the number of Leydig cells declines.[20] However, most older men with low T levels do not have increased LH.

The mechanisms linking secondary hypogonadism and aging are complex. Production of GnRH decreases with age and GnRH/LH pulse amplitude diminishes.[21,22] In addition, androgen negative feedback suppression of LH secretion may be increased.[23] Sex hormone—binding globulin (SHBG) levels tend to rise in older men, causing free T levels to decline.[24] The levels of T are higher in the morning than in the evening and there is a dampening of this diurnal rhythm as men grow older.[25]

ADULT-ONSET HYPOGONADISM AND CO-OCCURRING CONDITIONS

Association With Common Comorbidities

Adult-onset hypogonadism more often occurs in men who have chronic disease states that are more common as men age, *making it difficult to separate the influence of comorbidities from the influence of aging*. High body mass index (BMI; calculated as the weight in kilograms divided by the height in meters squared), central adiposity, and the MetS are associated with low serum total T and to a

lesser extent low free T levels.[26-31] Low serum total T level predicts the development of central obesity and accumulation of intraabdominal fat.[26-29] Low total and free T levels are associated with an increased risk of developing MetS, independent of age and obesity.[26-29] Lowering serum T levels in men with prostate cancer by treatment with GnRH analogs increased body fat mass.[32] These data are derived from observational studies and from meta-analyses of these studies; definitive answers regarding the causal relationship between T levels and obesity and the MetS require properly designed and adequately powered longitudinal studies.

Ding et al[33] reported a meta-analysis of the relationship between diabetes, T, SHBG, and estradiol in cross-sectional and prospective studies. Cross-sectional studies revealed that T levels were significantly lower among men with DM2. Prospective studies indicated that men with higher T levels had a 42% lower risk of DM2. Men with higher SHBG levels had a 52% lower risk of DM2. Estradiol levels were significantly elevated among men with diabetes compared to nondiabetic men. Kupelian et al[34] analyzed data from the Massachusetts Male Aging Study and reported that low serum SHBG, low total T, and clinical AD were significantly associated with increased risk of developing MetS over time; this relationship was particularly strong among normal-weight, middle-aged men. Among veterans, men with low T levels had higher BMIs and were more likely to have diabetes than were men with normal T levels.[35] At a mean follow-up of 4.3 years, all-cause mortality was lower (20.1%) among men with normal T levels than among men with low T levels (34.9%). Corona et al[36] found a linear inverse relationship between the number of MetS components and the likelihood of having low T level.

In the EMAS, BMI was significantly associated with the risk for secondary hypogonadism.[4] In an overlapping population, Maseroli et al[6] found that most men with secondary hypogonadism had metabolic disease, with BMI of 30 kg/m^2 or more tripling the risk of LOH (defined as low T levels + sexual symptoms).[37] Among normal-weight men, only 1 of 6 men was diagnosed with LOH in contrast to nearly two-thirds of men with a BMI of more than 35 kg/m^2 who had low T levels and inadequate gonadotropins.

Men with other types of comorbidities also may present with AOH. The presence of 1 or more comorbidities was significantly associated with secondary hypogonadism in the EMAS.[4] In the Hypogonadism in Males study, men were significantly more likely to have hypogonadism if they also had diabetes, hypertension, hyperlipidemia, asthma/chronic obstructive pulmonary disease, and/or prostate disease compared with men without these conditions.[16] The presence of low T level, therefore, may be a marker of poor health and the possible presence of comorbidities.

Adult-Onset Hypogonadism and Human Immunodeficiency Virus

Testosterone deficiency is more common in human immunodeficiency virus (HIV)-infected males than in the general population.[38] The impairment of the HP axis in HIV-infected patients is suggested by low T levels in combination with inappropriately low or normal serum LH. The pathophysiologic causes and mechanisms of the HIV-associated AOH are likely multifactorial, and include (1) poor clinical or nutritional status, (2) use of certain prescription medications used to treat HIV, (3) illicit drugs including opiates and methadone, (4) pituitary dysfunction, (5) hepatitis C coinfection and other opportunistic infections, (6) advancing age and increasing length of time diagnosed with HIV, (7) changes in body composition, (8) increased levels of estradiol and increased levels of SHBG, (9) normal age-related declines, (10) low CD4 cell count, (11) high HIV viral load and disease progression, (12) lean body mass, (13) MetS, and (14) wasting lipodystrophy.[38-46]

Adult-Onset Hypogonadism and Medication Effects

Testosterone levels can be affected by many pharmacologic agents[47] that are frequently administered to or used by men (eg, opioids, glucocorticoids, cimetidine, tricyclic antidepressants, nicotine, and marijuana). Men who use high doses of anabolic steroids often find that their T levels fall to castrate levels after stopping these drugs.[48] Opiate medications have an inhibitory effect on the HPG axis, resulting in a dose-dependent decrease

Mayo Clin Proc. ■ July 2016;91(7):908-926 ■ http://dx.doi.org/10.1016/j.mayocp.2016.04.022
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in T levels.[49] Statin drugs have been implicated in hypogonadism, but the evidence is not yet definitive.[50] Chemotherapy can affect the testes directly and may be toxic to the Leydig cells, decreasing T production.[51]

Other Associations With AOH

Sleep Disruption. The relationship between sleep disorders and secondary hypogonadism is complex and multifactorial. Men with obstructive sleep apnea have a higher prevalence of secondary hypogonadism than do age-matched controls.[52] Obesity is a common link between the increased prevalence of sleep disorders and hypogonadism; however, some literature suggests that sleep apnea is an independent risk factor for hypogonadism. Greater degrees of nocturnal hypoxia predict lower T levels,[53] possibly because men with sleep apnea secrete blunted levels of LH during sleep.[54]

Stress. Stress also is associated with secondary hypogonadism. Stress is a process in which internal or external events threaten or challenge an organism's existence and well-being and stress responses occur that are directed toward reducing the event's impact.[55] The stress process can manifest itself physiologically as a proinflammatory state that, in turn, may cause HPG axis disruption. Extreme examples, such as critical illness including acute myocardial infarction, elective surgery, and brain injury, may dramatically reduce T levels.[56] Psychosocial stress and work-related stress also decrease T levels.[57,58]

EFFECTS OF TESTOSTERONE TREATMENT

Testosterone Treatment in Older Men

The Testosterone Trials included 3 main trials (the Sexual Function Trial, the Physical Function Trial, and the Vitality Trial) that evaluated the effects of T or placebo gel for 1 year in 790 men aged 65 years or older.[59] Most participants were obese (62.9%). In the Sexual Function Trial, the testosterone-treated group, but not the placebo-treated group, experienced significantly increased sexual activity, sexual desire, and significantly improved erectile function. In the Physical Function Trial, statistically similar percentages of men had an improvement of at least 50 m in the 6-minute walking test in the T- and placebo-treated groups but when men from all 3 trials were pooled, more men in the T-treated group had improvement compared with the placebo-treated group (20.5% of T-treated men vs 12.6% of placebo-treated men). Testosterone did not improve vitality in the Vitality Trial, but men treated with T reported better mood and lower depression levels than did men who were treated with placebo. Adverse event rates were similar between groups. With regard to cardiovascular events, the same number of men in each group had strokes (5 in each group) and myocardial infarction, stroke, or death from cardiovascular causes (7 in each group). Statistically similar numbers of men had myocardial infarctions (1 in the placebo group and 2 in the T group) and death from a cardiovascular cause (1 in the placebo group and 0 in the T group). The authors note that these findings are not definitive because the trial was not powered to detect small differences in cardiovascular disease (CVD) risk.

Effects of Testosterone Treatments on AOH-Associated Comorbidities: Diabetes, MetS, and Obesity

Studies of the effects of T on diabetes, MetS, and obesity have yielded mixed findings. The Birmingham, Lichfield, Atherstone, Sutton Coldfield, and Tamworth (BLAST) randomized controlled trial (RCT) administered injectable testosterone undecanoate (TU) or placebo for 30 weeks to hypogonadal men with DM2.[60,61] Glycated hemoglobin (HbA_{1c}) level was significantly reduced in T-treated patients compared with placebo-treated patients at 6 and 18 weeks but not at 30 weeks. Additional findings differed depending on whether patients had a diagnosis of major depression. Among nondepressed men, those treated with T had significant improvements in BMI, weight, waist circumference, International Index of Erectile Function — Erectile Function subscale scores, and Aging Males' Symptoms scores. Depressed men did not experience these benefits.

The Testosterone Replacement in Hypogonadal Men with Type 2 Diabetes and/or Metabolic Syndrome trial evaluated symptomatic hypogonadal men treated with T gel or placebo for 12 months.[62] During the first 6

months of the trial, patients were not permitted to change diabetic medication regimens. At 6 months, T-treated patients had reduced homeostasis model assessment of insulin resistance compared with placebo-treated patients (15.2%), reduced lipoprotein A, reduced high-density lipoprotein, and improved International Index of Erectile Function scores. Among MetS participants, T reduced lipoprotein A and low-density lipoprotein compared with placebo. During the second 6 months of treatment, among patients with DM2 a significant decrease in HbA_{1c} level occurred at month 9, but medication changes were permitted and the statistical significance of this difference was primarily the result of the placebo group's values increasing. There were no significant effects of T on other lipid parameters, abdominal obesity, percentage body fat, BMI, or waist circumference. Findings from this trial are difficult to interpret given the high dropout rate (54% of participants completed both phases) and the large number of patients who took unauthorized medications during phase I (~24%).

Kalinchenko et al[63] reported findings from 184 hypogonadal men with MetS treated with injectable TU for 30 weeks (the "Moscow" trial). Testosterone treatment resulted in significant improvements in body weight, BMI, waist circumference, and some serum inflammatory markers.

Several single-center RCTs also have examined effects of T treatment in men with DM2 and MetS. Aversa et al[64] reported that injectable TU for 24 months improved homeostasis model assessment of insulin resistance, serum inflammatory markers, and carotid intima media thickness in 50 symptomatic hypogonadal men with DM2 or MetS. The prevalence of MetS also was reduced in the T arm. This study was unblinded at 12 months because of significant differences in outcomes. Gianatti et al[65,66] reported on 88 men with well-controlled DM2 and symptomatic hypogonadism treated with injectable TU for 40 weeks. Patients treated with testosterone exhibited significant improvements in lean body mass and abdominal subcutaneous adipose tissue volume but not glycemic control.

Gopal et al[67] performed a smaller crossover design study with 22 men with hypogonadism and DM2 treated with injectable T or placebo for 3 months. There were no effects on insulin sensitivity, fasting plasma glucose, HbA_{1c}, lipid, or biometric parameters. However, this study is likely underpowered given the small sample size and of insufficient length to reliably detect effects of T.

Basu et al[68] evaluated elderly hypogonadal men who were not diabetic. Participants were administered placebo or T via patch (5 mg/d) for 2 years. Testosterone treatment did not improve carbohydrate tolerance or alter insulin secretion or action, glucose effectiveness, or the pattern of postprandial glucose metabolism. The authors suggest that T deficiency is unlikely to be the cause of age-related deterioration in glucose tolerance.

Finally, Finkelstein et al[69] investigated the physiological effects of gonadal steroids (T and estradiol) in 198 healthy men by suppressing endogenous T and estradiol with GnRH-analog goserelin acetate, replacing T in graded doses, and inhibiting aromatase with anastrazole. When aromatization was intact, fat accumulation began with mild gonadal steroid deficiency (a T level of ~300-350 ng/dL), whereas lean mass, thigh-muscle area, and muscle strength were preserved until gonadal steroid deficiency was more marked (a T level of ≤200 ng/dL). The authors suggest that AD accounted for decreases in lean mass, muscle size, and strength; estrogen deficiency primarily accounted for increases in body fat; and both contributed to the decline in sexual function.[69] These findings provide a physiological basis for interpreting T levels in young/middle-aged men and identifying the adverse consequences that are most likely to occur at various gonadal steroid levels. In particular, because lean mass, thigh-muscle area, and erectile function were reduced at a T dose (1.25 g/d) that elicited a mean serum level of approximately 200 ng/dL, T supplementation seems justified in men with T levels in this range. Most importantly, the finding that estrogens have a fundamental role in the regulation of body fat and sexual function, coupled with evidence from previous studies of the role of estrogen in bone metabolism and gonadotropin secretion, indicates that estrogen deficiency may contribute to some of the key consequences of male hypogonadism.

Effects of Lifestyle Interventions

Some evidence indicates that AOH can be managed by lifestyle changes and other

Mayo Clin Proc. ■ July 2016;91(7):908-926 ■ http://dx.doi.org/10.1016/j.mayocp.2016.04.022
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interventions that directly address comorbidities. Corona et al[70] performed a meta-analysis and reported that both dietary interventions and bariatric surgery were associated with a significant increase in total T and free T levels. Increases were greater for bariatric surgery, which also induced a greater weight loss. Heufelder et al[71] reported in the Diabetes Management by Lifestyle and Testosterone study on a comprehensive lifestyle intervention (ie, diet and exercise) with or without the use of T gel among men with DM2 and MetS. At 1 year, both interventions improved serum T, HbA_{1c}, fasting plasma glucose, high-density lipoprotein cholesterol, triglyceride concentrations, and waist circumference. These improvements were greater in the lifestyle + T group, with 81.3% of the lifestyle + T group reversing MetS status compared with approximately one-third of the lifestyle-only group ($P<.05$).

In a longitudinal evaluation of EMAS data, a greater than 15% loss in BMI was associated with a significant increase in total T, free T, and LH levels[9]; only a very small number of men (n=22; <1%) lost this amount of weight during study follow-up. Additional studies have found that weight loss regardless of modality increases both total and free T levels.[12-14,72,73]

TESTOSTERONE MEASUREMENT

There are many challenges to the accurate laboratory diagnosis of AOH. These issues include physiological variation, the impact of age and obesity, methodological issues within and across assays and laboratories, and the difficulty of establishing with certainty what constitutes the "normal" range.

Circulating T levels vary substantially among healthy men and are influenced by episodic and diurnal fluctuations, day-to-day and seasonal variations, the presence of acute and chronic illness, and medications.[74] These factors may account for the intraindividual variability of approximately 10% on samples drawn from the same person at the same time of day 1 to 3 days apart or 3 months apart in the BACH study.[75] Diurnal variations also are substantial. Late afternoon levels are about 20% lower than morning values in young men but the difference may be as high as 50%. The difference is much smaller in older men.[76] Reference ranges are generally based on morning samples.

Concentrations of SHBG are a major determinant of total T levels. Factors that increase SHBG include aging, hyperthyroidism, estrogens, HIV disease, hepatitis C, alcoholic cirrhosis, and the use of anticonvulsants.[77,78] Disorders in which SHBG concentrations are low include obesity, DM2, hypothyroidism, nephrotic syndrome, acromegaly, and those involving the use of androgenic steroids. The mechanism through which visceral adiposity and insulin resistance result in low SHBG levels is not well understood[79,80] but is key to understanding low T levels in men with AOH.

Measurement is further complicated by differences across assay methodologies. Although most hospital laboratories now use automated platforms and an immunoassay with chemiluminescent detection, differences in affinity and specificity of the antisera used result in between-laboratory variation especially at low T values. Therefore, reference laboratories have adopted gas or liquid chromatography-mass spectrometry methods, which are sensitive and more specific, but are technically demanding and more costly. In one study, the variability in total T results among liquid chromatography-mass spectrometry assays was 15%, which is substantially less than that for immunoassays.[81]

Laboratories also differ in their definition of the normal range. Large populations of healthy men from young adulthood to the elderly have been studied, and the clinician should use a laboratory with a large database. The range of values can make interpretation challenging and the varying lower limits affect whether a man is identified as hypogonadal. Useful information regarding reference ranges and definitions also can be found in Le et al[82] and Paduch et al.[2]

Sex Hormone–Binding Globulin and Free T

The production of SHBG is controlled by numerous metabolic and hormonal factors.[79,80] The levels of SHBG are low in inflammatory states including obesity and insulin resistance, and low levels predict the development of MetS and DM2. High SHBG levels are found in patients with hyperthyroidism and hepatitis C, and with oral estrogen treatments.

Approximately 40% to 50% of the circulating T in men is SHBG-bound. According to the "free hormone hypothesis," SHBG-bound steroids do not enter cells but rather the non–SHBG-bound fraction (albumin bound + free) is biologically active; this fraction has been termed "bioavailable T." Because SHBG binds T with high affinity, the level of SHBG is a major determinant of the circulating total T level, and the level of SHBG and its affinity for T are used to calculate the free or bioavailable T concentration, which can also be determined by equilibrium dialysis. We agree with the Endocrine Society recommendation that clinicians may choose to calculate free T levels using total T and SHBG levels and albumin in the absence of access to the appropriate measurement technologies.

In men with AOH, the SHBG level may be low, especially if the patient is obese or insulin resistant or diabetic. In these men, who comprise a substantial portion of the men evaluated for AOH, the free or bioavailable T level may be normal while total T level is low, and the patient may not be T deficient. In this setting, a low total T level alone may overdiagnose AOH and free or bioavailable T level may be a better measure of gonadal status. Men with conditions that may result in low SHBG levels should be evaluated using an assay for free or bioavailable T. Methods include ammonium sulfate precipitation of SHBG-bound T, equilibrium dialysis, or a mass action equation to calculate these values from the levels of total T and SHBG. Direct analog assays for free T are readily automated but are inaccurate and give much lower results than do other methods and are not recommended.[83]

CLINICAL SIGNS AND SYMPTOMS OF AOH

Adult-onset hypogonadism is an often overlooked condition because hypogonadal men often ignore their symptoms.[84] The clinical signs and symptoms of AOH are variable and nonspecific and have a gradual onset with slow progression[1,11,85,86] (see Table 1). Because T influences all the steps of the male sexual response cycle, sexual dysfunction is common and can be the presenting symptom of AOH. These symptoms may include hypoactive sexual desire, reduced nocturnal and morning erections, reduced sex-induced erections, delayed ejaculation, and reduced semen volume.[16,85] The clinical practice guidelines of the Endocrine Society and the American Association of Clinical Endocrinologists as well as other authors suggest that physicians should measure the T levels of men with any of the symptoms and signs given in Table 2.

The physical examination may not be helpful in making an AOH diagnosis. However, small testicular size, alterations in testicular consistency and hair distribution, gynecomastia,

TABLE 1. Clinical Signs, Symptoms, and Conditions Consistent With Adult-Onset Hypogonadism and Low Testosterone Levels[1,11,85,86]

Most specific signs/symptoms	More general signs/symptoms	Conditions commonly associated with low testosterone level and adult-onset hypogonadism
Reduced sexual desire & activity	Decreased energy, motivation, initiative	Type 2 diabetes
Decreased spontaneous erections	Delayed ejaculation	Metabolic syndrome
Erectile dysfunction	Reduced muscle bulk & strength	Chronic obstructive lung disease, obstructive sleep apnea syndrome
Hot flushes/sweats	Diminished physical or work performance	End-stage renal disease, hemodialysis
Decreased testicle size	Mild anemia (normocytic, normochromic)	Osteoporosis
Loss of pubic hair, reduced shaving requirement	Depressed mood, irritability	Human immunodeficiency virus–associated weight loss
Increased body mass index, visceral obesity	Poor concentration & memory	History of infertility, cryptorchidism, pituitary disease, delayed puberty
Height loss, low trauma fractures, reduced bone mineral density	Sleep disturbances, sleepiness	Treatment with opioids or glucocorticoids

Mayo Clin Proc. ■ July 2016;91(7):908-926 ■ http://dx.doi.org/10.1016/j.mayocp.2016.04.022
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and small prostate size can be detected in some men with AOH. Changes in body composition and, in particular, an increase in visceral obesity often characterize AOH, while alterations in cognition, spatial memory, and mood may be present but less reliably predict AOH.[85]

Sexual symptoms may be the most helpful in identifying men likely to have AOH. In their second psychometric validation of the New England Research Institutes hypogonadism screener, Rosen et al[86] found that decreased spontaneous erections and low libido were the most prevalent clinical symptoms in both younger and older men. In addition to these 2 symptoms, difficulty getting or maintaining an erection was a symptom that significantly discriminated the low T group from the control group in the 2 age categories.[86]

In the EMAS, 3 additional nonsexual symptoms, that is, the inability to perform vigorous activity, fatigue, and depression, were also significantly related to low T levels. The most prevalent nonsexual symptoms of AOH in the Rosen study[86] were fatigue, muscle weakness, depressed mood, and increased body fat. Other nonsexual symptoms that significantly discriminated the T deficiency group from the control group were excessive irritability and difficulties remembering things read and directions.[85]

Men can be classified as having AOH if they have signs and symptoms of AOH and persistently low T levels without confounds to T measurement (ie, altered SHBG levels—see next section). Therefore, the signs and symptoms of low T level should be used in conjunction with biochemical parameters (ie, total T, free and/or bioavailable T, SHBG as appropriate; see Figure 4) to identify the syndrome.[1]

EVALUATION, DIAGNOSTICS, AND MONITORING

It is critical that men presenting with possible signs and symptoms of AOH be systematically evaluated, accurately diagnosed, carefully counseled regarding the risks and benefits of treatment, and followed regularly if testosterone therapy (TT) is initiated. The process recommended by the panel is summarized in Figure 4.

Patients presenting with possible signs and symptoms of AOH should have a history and physical examination and morning total T level measured by a reliable assay. Men who are acutely or subacutely ill may have a low T level because of illness and their evaluation should be deferred. A low or borderline low total T value should be interpreted in the context of other known causes of low T level (eg, medication effects). If a low value is found, then a second morning total T level should be measured in conjunction with LH and FSH values to assess for testicular vs HP components of hypogonadism. The SHBG levels should be measured if there is reason to suspect an SHBG abnormality (eg, in overweight or obese men)[87]; in this case, free T or bioavailable T level should be assessed.

If the T level is low and the LH level is elevated, then the patient has primary hypogonadism. If the T (and free/bioavailable T when indicated) level is low and LH + FSH levels are low or normal and the patient has signs and symptoms of AOH, then the patient may have AOH. If the total T level is extremely low (ie, <150 ng/dL), then an endocrine pituitary workup including prolactin and a magnetic resonance imaging study is indicated. If no cause is identified, then a trial of TT after exclusion of contraindications and with lifestyle modifications and comorbidity management is appropriate. The panel strongly recommends that TT be combined with lifestyle modifications (eg, dietary changes, exercise, and stress management) if the patient is overweight or obese, deconditioned, or sedentary, has other comorbidities such as hypertension or dyslipidemia, and/or reports elevated psychosocial stress levels. Patients who report signs or symptoms consistent with sleep apnea should be referred as necessary for the management of this condition. Obesity, DM2, and other comorbidities should be managed medically as necessary to

TABLE 2. Conditions in Which Serum T Level Measurement Is Suggested[1,11,86]

Infertility
Osteoporosis, low trauma fracture
Type 2 diabetes
Glucocorticoids, ketoconazole, opioid or other medications that affect T metabolism or production
Moderate to severe chronic obstructive pulmonary disease
Sellar mass, radiation to the sellar region, or other diseases of the sellar region
End-stage renal disease, maintenance hemodialysis
Human immunodeficiency virus–associated weight loss

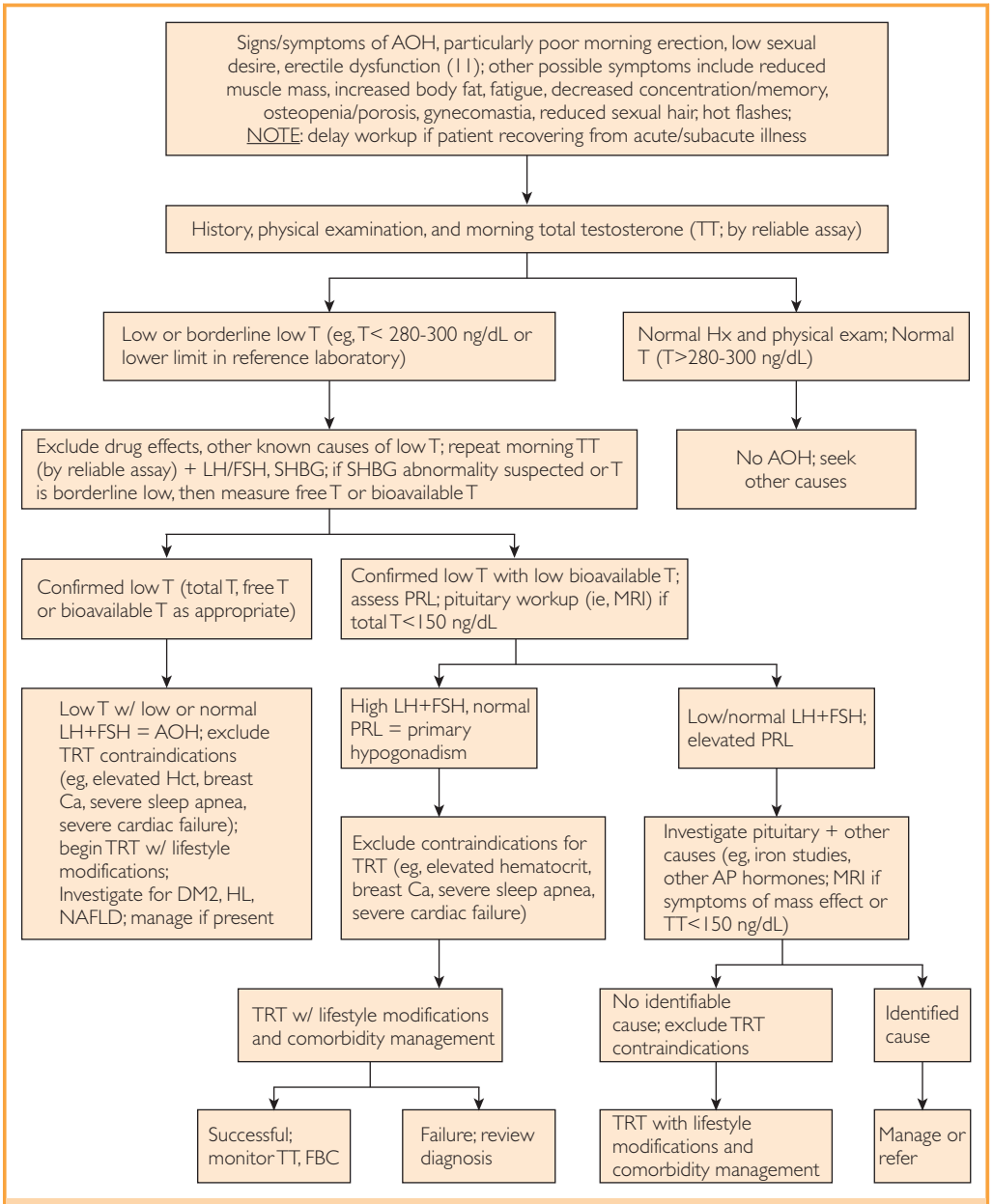

FIGURE 4. Diagnostic algorithm for the man presenting with signs and symptoms of AOH. AOH = adult-onset hypogonadism; AP = anterior pituitary; Ca = cancer; DM2 = type 2 diabetes; FBC = full blood count; HL = hyperlipidemia; Hx = history; LH = luteinizing hormone; FSH = follicle-stimulating hormone; Hct = hematocrit; MRI = magnetic resonance imaging; NAFLD = nonalcoholic fatty liver disease; PRL = prolactin; SHBG = sex hormone–binding globulin; T = testosterone; TRT = testosterone replacement therapy; TT = testosterone therapy.

optimize the patient's overall health and to maximize the potential positive impact of TT.

Once a man commences a trial of TT, he should be followed regularly for TT effectiveness and for adverse events. The panel endorses the timing and content of the Endocrine Society's guidelines for monitoring of patients on TT (see Figure 5).

Monitoring: Risks and Safety of T Treatment

There are 2 challenges to understanding the risks and safety of T treatment in

Mayo Clin Proc. ■ July 2016;91(7):908-926 ■ http://dx.doi.org/10.1016/j.mayocp.2016.04.022
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appropriately selected and counseled men. The first challenge is the lack of definitive evidence derived from properly designed and powered prospective studies. The second challenge is the existence of mixed evidence that is not definitive from the literature that is available. These challenges are highlighted below. The panel notes that in the absence of definitive evidence regarding risks, patients must be monitored regularly for T efficacy and adverse events.

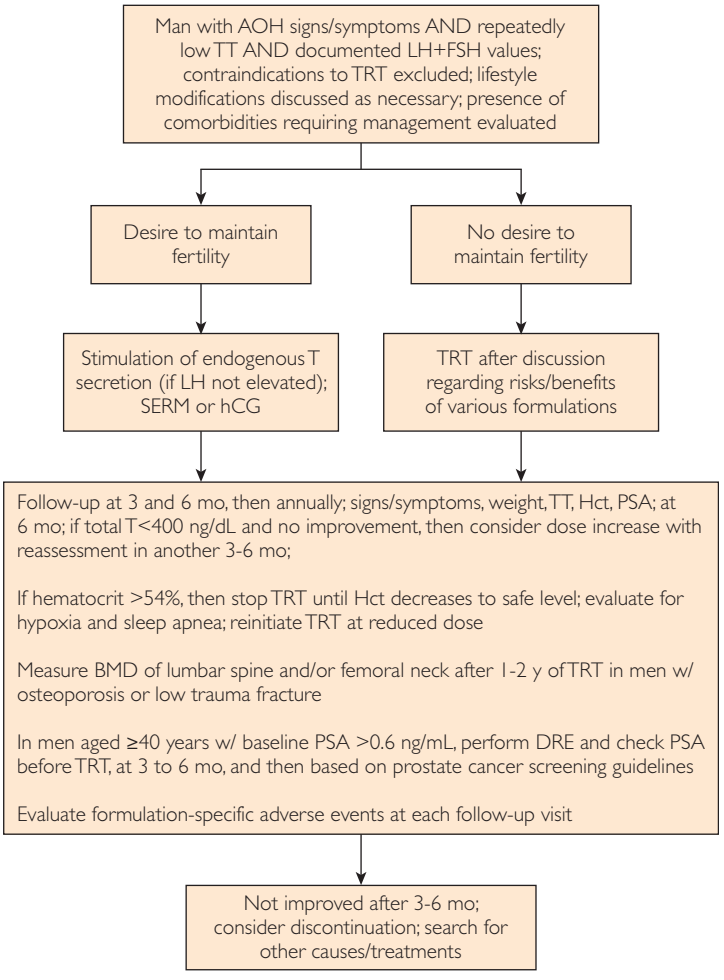

FIGURE 5. Treatment and follow-up algorithm for the patient with documented signs and symptoms of AOH who is administered TT. AOH = adult-onset hypogonadism; BMD = bone marrow density; hCG = human chorionic gonadotropin; Hct = hematocrit; LH = luteinizing hormone; FSH = follicle-stimulating hormone; PSA = prostate-specific antigen; SERM = selective estrogen receptor modulators; T = testosterone; TRT = testosterone replacement therapy; TT = testosterone therapy. Adapted from *J Clin Endocrinol Metab*,[1] with permission.

Cardiovascular Risks

Association Between Endogenous T and CVD Risks. Low T levels are associated with an increased risk of CVD.[88,89] Meta-analyses suggest that T level is lower among patients with CVD[90] but conflict regarding whether low T level is associated with increased CVD-related mortality[90] or risks are similar for hypogonadal and eugonadal men.[91]

Cardiovascular Risks of TT. Several retrospective analyses have raised concern that T treatment may increase CVD risk.[92] Because of these concerns, the Food and Drug Administration recently required manufacturers of prescription T products to change their labeling to clarify the approved uses of these medications and to add information about a possible increased risk of heart attacks and strokes in patients who take T. Definitive evidence, however, regarding the short- and long-term cardiovascular risks of T treatment is not yet available because the published prospective trials were not designed or powered to examine cardiovascular end points. Findings reviewed below from meta-analyses that pooled findings across individual studies with these weaknesses, therefore, must be interpreted with caution.

Meta-Analyses. There are multiple published meta-analyses that evaluated possible CVD risks associated with T treatment. Challenges to interpreting findings across meta-analyses include that these publications varied in study inclusion criteria, outcomes evaluated, and data analytic strategies. In addition, most authors report that the methodological quality of the included trials was poor to moderate. A meta-analysis of 75 placebo-controlled randomized trials revealed no increase in CVD risk and a protective effect of T in men with metabolic disorders.[93] A meta-analysis of 24 placebo-controlled TT trials revealed no increased risk for major adverse cardiovascular events among men treated with T compared with men treated with placebo.[8] Another meta-analysis of 19 randomized placebo-controlled trials also reported no increased risk for any cardiovascular event among T-treated men compared with placebo-treated men.[94] Fernández-Balsells et al[95] conducted a

meta-analysis of comparative, randomized, and nonrandomized studies and reported no differences between T-treated men and non–T-treated men in all-cause mortality, need for coronary bypass surgery, or myocardial infarction.

Haddad et al[96] conducted a meta-analysis of 30 randomized placebo-controlled trials of TT and reported no significantly increased risk of CVD-related adverse events. However, although odds ratios (ORs) for any cardiovascular event (1.82; 95% CI, 0.78-4.23; $P>.05$) and for myocardial infarction (2.24; 95% CI, 0.50-10.0; $P>.05$), were nonsignificant, the ORs are large enough to call attention to the possibility that there may be CVD risk associated with TT. In this meta-analysis, men randomized to TT had twice the number of CVD-related adverse events as men in the placebo arm. An additional meta-analysis has reported that TT is significantly associated with an increased risk of CVD-related adverse events (OR, 1.54; 95% CI, 1.09-2.18; $P<.05$).[97] These authors also note that CVD risks appear to be higher in trials not funded by the pharmaceutical industry (OR, 2.06; 95% CI, 1.34-3.17).

The need for definitive trials that can yield unambiguous findings is underscored by several recent publications that report possible risks of TT. Specifically, Layton et al[98] reported findings from a retrospective cohort study using administrative insurance claims data. Men who received T injections had significantly higher rates of CVD events, hospitalizations, and death than did men who used T-containing gels; event rates for men using T-containing patches were similar to rates for gels. These data are potentially important but difficult to interpret because the study did not include assessment of whether men met criteria for TT (eg, were hypogonadal) or compare event rates to those in non–T-using men. Finkle et al[99] reported that T-treated men had a higher rate of nonfatal myocardial infarction in the 90 days after receiving a T prescription compared with the 12 months before the prescription. These data are also difficult to interpret because of the lack of a control group of untreated men with low T level and the use of a comparison group of men prescribed phosphodiesterase type 5 inhibitors. Furthermore, Vigen et al[92] reported that T-treated men had a higher rate of CVD adverse events (myocardial infarction, stroke, or death) compared with untreated men. These findings also are difficult to interpret given the statistical limitations of the analytic procedures.

Prostate Cancer

Although no appropriately designed and powered study has been conducted to assess prostate cancer–related risks of TT, the available evidence suggests that T treatment does not increase prostate cancer risk.

Low T levels are associated with higher rates of prostate cancer as well as more advanced prostate cancer tumor grade, stage, and volume compared with men who are not hypogonadal.[100,101] The incidence of prostate cancer in men being treated with T is reported as similar to the rate in untreated men in the general population.[102] A meta-analysis of 19 placebo-controlled TT studies in men with low or low-normal T level found no difference in prostate biopsies, prostate cancer occurrence, or rise in prostate-specific antigen (PSA) level compared with men treated with placebo; however, men administered T had a significantly higher rate of all prostate events (prostate cancer + increased PSA levels + prostate biopsy).[94]

Observational studies also suggest that men taking T do not have an increased risk of developing prostate cancer. A large longitudinal study evaluating roughly 10,000 men found no association between androgen levels and prostate cancer risk.[103]

With regard to men after prostate cancer treatment, the available evidence is weaker, consisting predominantly of retrospective chart reviews. Low preoperative T levels may predict PSA recurrence after radical prostatectomy.[104] Men postradical prostatectomy administered T have been reported to have low PSA recurrence rates.[105] There is also a low PSA recurrence rate among men treated with T after radiation or brachytherapy.[106] A small study of men receiving T under active surveillance for prostate cancer has found no increased risk of prostate cancer progression.[107] Furthermore, some data suggest that T may be protective against the recurrence and progression of prostate cancer.[108-111] However, the available studies do not definitely address the risks and benefits

Mayo Clin Proc. ■ July 2016;91(7):908-926 ■ http://dx.doi.org/10.1016/j.mayocp.2016.04.022
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of T in men who have undergone prostate cancer treatment; this issue requires data from appropriately designed and powered prospective trials.

Benign Prostatic Hypertrophy/Lower Urinary Tract Symptoms

Although a 2007 multinational physician survey revealed that up to 18% of providers considered benign prostatic hypertrophy (BPH) risk with T administration as very important,[112] no clinical trials demonstrate that TT worsens BPH/lower urinary tract symptoms.[113] No difference in prostatic androgens were found between men with and without BPH.[114] Placebo-controlled trials of exogenous administration of dihydrotestosterone (DHT) and T resulted in no changes in prostate DHT or T in blood sampling or prostate biopsy specimens.[115-117] Both T and DHT have anti-inflammatory properties in the prostate.[118] Finally, several studies demonstrate either no change or improvement in BPH/lower urinary tract symptoms with T administration.[119-125]

Infertility

Testosterone treatment is a form of male birth control. Through negative feedback mechanisms exogenous T suppresses endogenous LH and FSH production, which results in testicular atrophy and severe oligospermia or absolute azoospermia typically within 3 to 4 months of use. Trials testing T as a form of male contraception revealed sperm concentrations of less than 1 million/mL in 95% of men on injections and 90% on gels.[126,127] Testis atrophy occurs with mean loss of 4 to 5 mL of testis volume from suppression of both seminiferous tubule volume and Leydig cell volume.[128] Recovery of spermatogenesis after discontinuation of T treatment is dependent on the duration and intensity of treatment along with baseline fertility status. In a study of 271 men, median time to regain sperm counts of more than 20 million was 3.7 months and only 46% returned to baseline at an average of 6.7 months.[126] It is critical to understand that men with impaired fertility before the initiation of TT may remain permanently azoospermic.[128] All men of child-bearing age should be asked before the initiation of TT whether they are considering fathering children. A recent disturbing study revealed that 25% of urologists reported using T to treat infertility.[129]

Erythrocytosis

Androgens have an erythrogenic effect,[130] with elevations in hemoglobin (Hb) and hematocrit (Hct) levels being the most frequently encountered sequelae of TT.[94,95,131] The increase in Hct level is dependent on both dose and serum level.[132-134] During TT, levels of Hb and Hct rise for the first 5 to 6 months, then tend to plateau[135,136]; levels decline to baseline within 3 to 12 months after TT discontinuation.[137,138] Of all T formulations, injectables are associated with the greatest treatment-induced increases in Hb and Hct levels.[139-142]

Although it has been hypothesized that enhanced blood viscosity poses a threat for ischemic sequela, the direct relationship between TT-induced erythrocytosis and subsequent risk for cardiovascular events, including stroke and deep vein thrombosis, has not been found through prospective RCTs.[143-147] In a recently published meta-analysis of all RCTs examining the association between TT and cardiovascular risk, Corona et al[93] noted that the data do "not support a causal role between testosterone supplementation and adverse cardiovascular events when hypogonadism is properly diagnosed and replacement therapy correctly performed." The panel notes, however, that as with other potential risks associated with TT, definitive answers can be derived only from high-quality trials designed to answer these questions; the data reviewed here cannot provide these answers.

Currently, the Endocrine Society Clinical Practice Guidelines state that Hct values higher than 54% warrant discontinuation of TT until further assessment. If the Hct levels become markedly elevated, phlebotomy should be considered for expedited normalization of levels. Finally, patients newly diagnosed with hypertension either before or during TT warrant close monitoring.[1]

CONCLUSION

Adult-onset hypogonadism, both as a term and as a conceptual distinction among hypogonadal syndromes, has raised considerable debate. Clinical evidence supports the authenticity of

this entity and its health relevance. Given this perspective, it is important to acknowledge gaps in the understanding of this syndrome and its treatment. Ongoing research efforts should focus on epidemiology, disease risk associations, pathophysiology, molecular pharmacotherapeutics, and health-related outcomes of its diagnosis and treatment. Importantly, improved clinical management can be expected to result from ongoing rigorous investigation of diagnostic criteria and demonstration of efficacy and safety of treatments for this syndrome.

ACKNOWLEDGMENT

We gratefully acknowledge the invaluable guidance of Shehzad Basaria, MD, in preparation of the manuscript.

Abbreviations and Acronyms: **AD** = androgen deficiency; **AOH** = adult-onset hypogonadism; **BACH** = Boston Area Community Health; **BMI** = body mass index; **BPH** = benign prostatic hypertrophy; **CVD** = cardiovascular disease; **DHT** = dihydrotestosterone; **DM2** = type 2 diabetes; **EMAS** = European Male Ageing Study; **FSH** = follicle-stimulating hormone; **GnRH** = gonadotropin-releasing hormone; **Hb** = hemoglobin; **HbA_{1c}** = glycated hemoglobin; **Hct** = hematocrit; **HP** = hypothalamic-pituitary; **HPG** = hypothalamic-pituitary-gonadal; **LH** = luteinizing hormone; **LHRH** = luteinizing hormone-releasing hormone; **LOH** = late-onset hypogonadism; **MetS** = metabolic syndrome; **OR** = odds ratio; **PSA** = prostate-specific antigen; **RCT** = randomized controlled trial; **SHBG** = sex hormone—binding globulin; **T** = testosterone; **TT** = testosterone therapy; **TU** = testosterone undecanoate

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Grant Support: The colloquium from which this manuscript originated was funded by a grant from the Sexual Medicine Society of North America (SMSNA) Foundation and an educational grant from Repros Therapeutics, Inc. The SMSNA required complete independence from industry during the development of this document. No industry representatives were present in the closed meeting, there was no industry participation in the evidence selection, discussion, or creation of this document, and there was no attempt by industry to influence its content.

Potential Competing Interests: Dr Khera is a consultant for AbbVie, Endo Pharmaceuticals, Lipocine, and Repros Therapeutics, Inc. Dr Carson received grant support from Auxilium and is a consultant for AbbVie. Dr Dobs received grant support from the National Institutes of Health and Boehringer Pharmaceuticals. Dr Goldstein is on the advisory board of Lipocine and TesoRx and is involved in research with Endo, Lipocine, Repros, and TesoRx. Dr Hellstrom is a consultant for Endo, Repros Therapeutics, and Lipocine. Dr Kacker is founder/owner of MHB Labs. Dr Köhler is involved in research with and is a consultant for AbbVie and Lipocine. Dr Mills is a speaker for AbbVie. Dr Miner is a consultant for Lipocine and Repros Therapeutics. Dr Sadeghi-Nejad is a clinical research investigator for Endo. Dr Burnett is involved with Auxilium, AbbVie, and Lilly. The rest of the authors report no competing interests.

Consensus statement: Adult-onset hypogonadism is a measurable syndrome characterized by low testosterone, associated symptoms, and low or normal gonadotropin levels. Men with adult-onset hypogonadism who are candidates for treatment with testosterone should be counseled regarding the benefits and risks of treatment. Patients who are treated should be monitored regularly.

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