Men's Health, Low Testosterone, and Diabetes

Individualized Treatment and a Multidisciplinary Approach

Abstract

Testosterone plays a critical role in male reproductive and metabolic functioning. Serum testosterone levels decrease with age, and low testosterone is associated with a variety of comorbidities, including insulin resistance, type 2 diabetes, obesity, metabolic syndrome, and cardiovascular disease. Men with type 2 diabetes have been shown to have significantly lower testosterone levels than men without diabetes. Several forms of testosterone replacement therapy (eg, oral, injectable, buccal, transdermal preparations) are available for use in the United States. The primary goals of testosterone therapy are to restore physiologic testosterone levels and reduce the symptoms of hypogonadism. Testosterone therapy may be a viable option in some men with diabetes and low testosterone; however, clinicians must be aware of contraindications to therapy (eg, prostate cancer and male breast cancer), implement appropriate monitoring procedures, and ensure that patient expectations are realistic regarding treatment outcome. Data suggest that testosterone therapy may have a positive effect on bones, muscles, erythropoiesis and anemia, libido, mood and cognition, penile erection, cholesterol, fasting blood glucose, glycated hemoglobin, insulin resistance, visceral adiposity, and quality of life. Sexual health may be a window into men's health; thus, more effective communication strategies are needed between clinicians and men with diabetes to ensure that sexual health topics are adequately addressed. Diabetes educators can play a key role in screening for low testosterone, providing relevant information to patients, and increasing clinician awareness of the need to address men's sexual health and implement appropriate strategies. Multidisciplinary care and individualized treatment are needed to optimize outcome.

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Advancing age is well recognized as a cause of reduced serum testosterone levels, even after controlling for age-related chronic conditions.[1] In addition, low testosterone (low T) is associated with numerous comorbidities, such as insulin resistance,[2,3] type 2 diabetes,[1,3,4] obesity,[1] metabolic syndrome,[4] and cardiovascular disease.[2] Clinical trial evidence suggests that men with diabetes have significantly lower testosterone levels than men without diabetes,[5] yet testosterone screening is not routinely performed as a part of diabetes care.[6] Based on suggested evidence, the goal of this continuing education program is to enable proactive management of low T through the initiation of replacement therapy to improve patient quality of life and to integrate emerging strategies of clinical care and management of low T in diverse practice settings.

Most professional organizations suggest that low T findings should be part of the diagnosis of hypogonadism,[7] a clinical syndrome caused by failure of the testes to produce physiological levels of testosterone and adequate spermatozoa.[8] Although screening instruments[9,10] and general guidelines[8,11,12] are available to aid clinicians in the diagnosis of low T and hypogonadism, more accurate screening/diagnostic tools and corresponding treatment protocols are needed in men with diabetes who have low T.[6] Other barriers associated with the identification and management of low T in men with diabetes include lack of patient-clinician communication; lack of patient awareness; patient embarrassment; inadequate provider knowledge; personal, cultural, or gender issues; a focus on acute care; and the current structure of diabetes education programs.[6]

Several forms of testosterone replacement therapy (eg, oral, injectable, buccal, and transdermal preparations) are currently available for use in the United States,[13] the main goals of which are to restore physiologic testosterone levels and to reduce the symptoms of hypogonadism.[4] Testosterone therapy may be a viable option in some men with diabetes and low T; however, clinicians must be aware of contraindications to therapy (eg, prostate cancer and male breast cancer),[4,14] implement appropriate monitoring procedures,[13-15] and ensure that patient expectations are realistic regarding treatment outcome.[6] Furthermore, current testosterone preparations differ in terms of ease of administration, patient preference, potential risks, and safety profiles[13]; thus, individualized treatment is needed to optimize outcomes. Data suggest that testosterone therapy could potentially have a positive effect on bones, muscles, erythropoiesis and anemia, libido, mood and cognition, penile erection, cholesterol, fasting blood glucose level, glycated hemoglobin, insulin resistance,[16] visceral adiposity,[17] and quality of life.[18] New testosterone replacement products are in the pipeline and may serve to improve the perceived deficiencies of current therapies.[19]

The Physiology and Function of Testosterone

Testosterone is a cholesterol-based steroid hormone that plays a key role in numerous biological functions throughout the male life cycle.[20,21] In the seventh week of male fetal development, Leydig cells are formed and begin to produce testosterone, which drives the development of the vas deferens, epididymis, and seminal vesicles.[21] The external genitalia are masculinized by testosterone at 8 weeks.[21]

Testosterone begins to influence the development of secondary male sex characteristics and several anabolic processes during the pubescent period[21] (see Table 1). At this time, the secretion of gonadotropin-releasing hormone from the hypothalamus causes the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary.[21] Leydig cells produce testosterone in response to the release of LH, which results in the development of male secondary sex characteristics.[21] Gonadotropin-releasing hormone and LH/FSH secretion decreases as the testosterone level increases; of note, the hypothalamic-pituitary axis is regulated by a negative feedback loop.[21]

After physical maturity has been attained, testosterone aids in erectile function, sustains spermatogenesis, and maintains secondary sex characteristics.[21] Testosterone also exerts a stimulatory effect on bones, muscles, erythropoiesis, mood, and cognition.[16]

Defining the Terms: Low T, Hypogonadism, and Testosterone Deficiency Syndrome

Testosterone is the main circulating androgen in the human male.[19] The testis, which secretes more than 95% of circulating testosterone, produces 6 to 7 mg of the hormone per day[19]; a small amount of testosterone is secreted from

Table 1

Anabolic and Androgenic Functions of Testosterone

Androgenic Functions	Anabolic Functions
Influences male reproductive tract and secondary sex characteristics	Promotes growth of somatic tissue
Erections	Formation of bone
Ejaculation	Erythropoiesis
Libido	Prostate growth
Prenatal differentiation	Muscle bulk

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the adrenals.[22] Testosterone is metabolized to dihydrotestosterone by 2 forms of 5-alpha reductase in the prostate and skin or to estradiol by aromatase in adipose tissue.[22]

The normal range of total testosterone is 300 to 1000 ng/dL (10.4-34.7 nmol/L).[18] Most professional organizations suggest that a low T level should be part of the diagnosis of hypogonadism,[7] a clinical syndrome caused by the failure of the testes to produce physiological levels of testosterone and adequate spermatozoa due to the disruption of 1 or more parts of the hypothalamic-pituitary-gonadal axis.[8] Guidelines are inconsistent with regard to the level of total testosterone that defines hypogonadism,[18,23] but the definition suggested by the American Association of Clinical Endocrinologists for hypogonadism is a testosterone level of <200 ng/dL (6.9 nmol/L).[11,18]

Classic hypogonadism is generally stratified into 2 categories (primary and secondary) based on causes and characteristics. Primary hypogonadism is caused by testicular failure (congenital or acquired)[24] and is characterized by decreased testosterone and increased LH and FSH.[16] Secondary hypogonadism is caused by inadequate secretion of either pituitary gonadotropins or hypothalamic gonadotropin-releasing hormone[24] and is characterized by decreased testosterone and normal or decreased LH and FSH[18] (see Table 2).

Much debate surrounds the terminology used to describe the condition caused by a decline in testosterone.[25] Many terms, such as *male climacteric*, *male menopause*, *andropause*, *androgen decline in the aging male*, *partial androgen decline in the aging male*, and *late-onset hypogonadism*, imply that the condition occurs late in life.[15] Some clinicians suggest that these terms do not accurately depict the condition, given that testosterone decline can begin in men as young as 40 years old.[25] In contrast, a recently proposed term—*testosterone deficiency syndrome* (TDS)—allows a broader definition that is not solely associated with older age.[25] TDS refers to the signs and symptoms that occur in men with abnormally low T.[25]

Table 2

Possible Causes of Primary and Secondary Hypogonadism

Primary hypogonadism	Klinefelter syndrome
	Androgen receptor defects
	5-alpha reductase deficiency
	Myotonic dystrophy
	Cryptorchidism
	Hemochromatosis
	Mumps orchitis
	Aging
	HIV
	AIDS
	Other chronic diseases
Secondary hypogonadism	Kallmann syndrome
	Fertile eunuch syndrome
	Pituitary disorders
	HIV
	AIDS
	Other chronic diseases

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Measurement and Interpretation of Testosterone Levels

Circulating endogenous testosterone can be free (2% to 3%), weakly bound to albumin (20% to 40%), or tightly bound to sex hormone–binding globulin (SHBG; 60% to 80%).[21,23] Both free and albumin-bound testosterone are bioavailable, whereas SHBG-bound testosterone is considered inactive and thus unavailable for use in the body.[21,23]

Laboratory measurement of testosterone can include total testosterone, bioavailable testosterone, and SHBG[18]; in addition, LH and FSH can be measured to distinguish between primary and secondary hypogonadism.[18] Measurement of total testosterone is the method used most often in clinical practice and research studies.[18] A recent study showing that free testosterone levels are low in one-third of men with diabetes[26] strengthens the case that free or bioavailable testosterone should be measured in this patient group.[23]

Testosterone secretion varies diurnally and is usually highest in the morning (6:00 AM to 8:00 AM) and lowest in the evening (6:00 PM to 8:00 PM)[27]; of interest, the circadian pattern of circulating testosterone may be absent or reduced in elderly men.[25] The preferred time for measurement of total testosterone is between 8:00 AM and 11:00 AM.[15,21] Testosterone levels are also higher in late summer and early autumn and lower in late winter and early spring.[27]

Testing that shows an abnormal testosterone level should be repeated, preferably in the morning.[4] If testosterone levels are confirmed to be abnormally low, measurement of LH and prolactin is warranted.[4] An elevated LH level suggests testicular dysfunction, whereas an elevated prolactin level may indicate the possibility of a pituitary tumor.[4] In addition, an increase in prolactin may inhibit gonadotropins, thereby causing secondary hypogonadism.[4]

Factors that can affect the interpretation of testosterone results in an aging male include the quality of the specimen, concomitant drug therapies, physiology, and analytical effects.[7] Notably, intraindividual variability within short time periods and interlaboratory fluctuations may be significant; thus, repeat measurement may be advisable in some men.[15]

Prevalence of Low T and Hypogonadism

A decrease in total testosterone with advancing age has been demonstrated in several longitudinal and cross-sectional studies.[24] Unlike women, who experience a rapid decline in female hormone production over a short period of time, men experience a more gradual decline in the production of male hormones.[28]

After age 30 years, the average annual decline in serum testosterone in men is about 1% to 2%[4,18]; however, testosterone levels vary widely among men, and normal testosterone levels are maintained by some men even into old age.[28] In the Baltimore Longitudinal Study of Aging, 20% of men in the seventh decade of life and 30% of men in the eighth decade were found to have low total testosterone levels.[29]

The prevalence of classic hypogonadism is about 1 in 200 adult men.[25] When bioavailable testosterone is measured, 2% to 5% of men in their 40s are defined as being hypogonadal, compared with 30% to 70% of men in their 70s.[25] In the Hypogonadism in Males study in 2162 men (mean age, 60.5 years; age range, 45-96 years), the prevalence of hypogonadism was 38.7% in men presenting to primary care offices. Furthermore, the risk of hypogonadism was shown to increase by 17% for every 10-year increase in age.[30]

The prevalence of TDS varies according to the definition used as well as the study design and population.[25] Overall, TDS prevalence ranges from 6% to 9.5% in community-dwelling men aged 40 to 70 years and increases to 15% to 30% in men who are obese or have diabetes.[25]

Causes of and Risk Factors for Low T

As men age, the pituitary gland becomes less responsive to hormonal signals, and Leydig cells become gradually desensitized and decline in number.[21] Erratic LH secretion with age further impedes hormonal signaling and leads to a reduction in available testosterone.[21] Reduced growth hormone levels contribute to a reduction in bone density and lean muscle mass.[21] Levels of dehydroepiandrosterone and dehydroepiandrosterone sulfate also decrease with age and may affect psychological aspects of aging.[21] SHBG increases significantly with age; in fact, SHBG in an 80-year-old man is twice that of a 20-year-old man.[1]

Interindividual differences exist in the onset and rate of testosterone decline; thus, the presentation of clinical hypogonadism may occur at different ages and to varying degrees.[21] Notably, hypogonadism may be underrecognized and undertreated, given that some symptoms (eg, loss of muscle mass) may be deemed to be part of the normal aging process.[21]

Low T is also associated with a variety of comorbidities, including insulin resistance,[2,3] type 2 diabetes,[1,3,4] metabolic syndrome,[4] obesity,[1] , osteoporotic fractures, and cardiovascular disease,[2] as well as reduced survival.[24] Other conditions associated with reduced T and/or increased SHBG levels include the use of certain medications, alcoholism (daily intake >40 g), and/or alcoholic liver disease.[1]

Insulin Resistance

Insulin resistance is central to several metabolic abnormalities that increase the risk of cardiovascular disease, including hyperlipidemia, hyperglycemia, and hypertension.[2] Hyperlipidemia is a key player in metabolic syndrome[31] and a risk factor for the development of type 2 diabetes.[32] Low serum testosterone concentration has been shown to be associated with increased insulin resistance[32,33]; however, the nature of the association has not been fully elucidated.[34]

In the Rancho Bernardo study, in 294 men aged 55 to 89 years, low T levels predicted insulin resistance; furthermore, the odds of developing incident type 2 diabetes were 2.7 (95% confidence interval [CI], 1.1-6.6) in men with total testosterone levels in the lowest quartile.[35] Results of a large cross-sectional study showed that low T levels were independently associated with insulin resistance in men with both type 1 and type 2 diabetes and that changes in testosterone levels and insulin resistance were inversely correlated.[36] The inverse correlation between testosterone and insulin resistance has been shown to be mediated through body fat, independent of SHBG.[33]

Diabetes

In 2007, 12.0 million of all US men aged 20 years and older (11.2%) had diagnosed or undiagnosed diabetes.[37] As mentioned above, data are now available on the role of endogenous testosterone in the development of both type 1 and type 2 diabetes; however, whether the relationship between low T and diabetes is direct or indirect remains unknown.[34]

In a systematic review and meta-analysis of cross-sectional studies, testosterone levels were found to be significantly lower in men with type 2 diabetes than in men without diabetes (mean difference, –76.6 ng/dL; 95% CI, –99.4 to –53.6).[5] In addition, a systematic review and meta-analysis of prospective studies showed that men with higher testosterone levels (ie, between 449.6 and 605.2 ng/dL) had a 42% lower risk of type 2 diabetes.[5] In a study comparing free testosterone concentration in 331 men with type 2 diabetes and 524 healthy men, levels were found to be lower in the former than latter group in each decade of life between the ages of 40 and 69 years.[3] A study in 434 men aged 50 to 86 years found that the incidence of type 2 diabetes was significantly higher in those with testosterone levels of <10 nmol/L.[38]

Results from a study sample in the Third National Health and Nutrition Examination Survey, which included 1413 adult men aged ≥20 years from the general population, found that men with free or bioavailable testosterone levels in the first (lowest) tertile were about 4 times more likely than men in the third tertile to have prevalent diabetes after adjustment for age, race/ethnicity, and adiposity.[39] Furthermore, the association of low levels of free or bioavailable testosterone with prevalent diabetes persisted after men with clinically abnormal testosterone (ie, total testosterone <3.25 ng/mL or free testosterone <0.07 ng/mL) were excluded.[39]

Prospective results from the Massachusetts Male Aging Study suggest that low T and SHBG levels may contribute to the development of type 2 diabetes.[34] The study consisted of a population-based random sample of men aged 40 to 70 years who enrolled in the study between 1987 and 1989 (n = 1709) and were followed for 7 to 10 years (n = 1156).[34] Testosterone and SHBG levels at enrollment were used to predict new cases of diabetes between enrollment and follow-up.[34] The investigators reported that after controlling for confounding factors, diabetes at follow-up was predicted jointly and independently by lower baseline levels of free testosterone and SHBG.[34] The odds ratios in favor of future diabetes were 1.58 for a decrease of 1 standard deviation in free testosterone and 1.89 for a decrease of 1 standard deviation in SHBG.[34]

A study comparing testosterone levels in 50 men with type 2 diabetes (age range, 28-51 years) and 50 men with type 1 diabetes (age range, 23-58 years) found that mean total testosterone concentration was significantly lower in the former than latter group. Of interest, in men with type 1 diabetes, mean total testosterone, free testosterone, and bioavailable testosterone levels were in the middle of the normal range.[40]

Metabolic Syndrome

Metabolic syndrome, a constellation of clinical findings that include dyslipidemia, central visceral obesity, hypertension, and hyperinsulinemia,[41] is on the rise in both developed and developing countries.[31,42] Low total testosterone has been shown to be correlated with an increased risk of developing metabolic syndrome,[43] an inverse relationship that seems to be consistent across all race and ethnic groups.[41,44] Furthermore, the individual components of metabolic syndrome are more prevalent in men with hypogonadism.[43] In contrast, higher levels of testosterone in

middle-aged and aging men have been associated with protection against the development of metabolic syndrome.[41]

Data suggest a relationship between metabolic syndrome and cardiovascular morbidity and mortality.[43] Indeed, individuals with metabolic syndrome are 3 times more likely than those without the syndrome to develop cardiovascular disease.[42] Early testosterone measurement may help to identify men with the greatest risk of developing metabolic syndrome as a precursor of cardiovascular disease.[41]

Some investigators have proposed that the coexistence of hypoandrogenemia (hypogonadism, hypotestosteronemia) and metabolic syndrome should be considered a separate entity, the hypoandrogen-metabolic syndrome.[31] Characteristics common to hypotestosteronemia and the metabolic syndrome include increased low-density lipoprotein cholesterol, triglycerides, blood pressure, fibrinogen, plasminogen activator inhibitor–1, fasting glucose, fasting insulin, visceral adiposity, and decreased high-density lipoprotein cholesterol.[31] Of interest, the same characteristics are also found in individuals who are obese.[31]

Obesity

The relationship between abdominal (central or waist) adiposity and low T, especially the direction of causality, has not yet been clearly elucidated.[1] Nonetheless, 2 cross-sectional studies have demonstrated an inverse relationship between waist circumference and low T.[23,45] A study of 355 men aged >30 years with type 2 diabetes found that bioavailable and total testosterone levels were significantly lower in men with a body mass index (BMI) >30 kg/m^2 or waist circumference >94 cm.[23] In a study of 400 men (age range, 40-80 years) randomly selected from a population-based sample, increases in both waist circumference and BMI were correlated with low bioavailable testosterone, total testosterone, and SHBG.[45]

Other study data have demonstrated that men with increasing abdominal or total adiposity experience reduced levels of free and total testosterone.[1,46,47] Furthermore, a study of 50 men with type 2 diabetes (age range, 28-51 years) and 50 men with type 1 diabetes (age range, 23-58 years) found that total, free, and bioavailable testosterone concentrations were negatively correlated with BMI in men with both types of diabetes.[40]

Osteoporotic Fracture

One-third of osteoporotic fractures occur in men, thus identifying that fracture risk factors may aid in the implementation of appropriate prevention strategies to reduce disease burden.[48] The prospective Dubbo Osteoporosis Epidemiology Study of 609 community-dwelling men older than 60 years (mean age, 72.6 years) showed that lower serum testosterone levels were independently correlated with an increased risk of osteoporotic fracture.[48] After adjusting for SHBG, both serum testosterone and serum estradiol levels were associated with overall fracture risk.[48] Furthermore, after additional adjustment for major fracture risk factors, lower testosterone was still correlated with increased risk of fracture, especially hip (hazard ratio [HR], 1.88; 95% CI, 1.24-2.82) and nonvertebral (HR, 1.32; 95% CI, 1.03-1.68) fractures.[48]

Cardiovascular Disease and Reduced Survival

The risk of cardiovascular disease is 2 to 5 times greater in patients with diabetes than in the general population, which is at least partly due to decreased androgen levels.[2] Cardiovascular disease is the leading cause of morbidity and mortality in patients with diabetes.[2]

One prospective population-based study in 794 men aged 50 to 91 years (median age, 73.6 years) found that men with testosterone levels in the lowest quartile (ie, <241 ng/dL) had a 40% increased risk of death compared with men who had higher levels, irrespective of preexisting health issues or other risk factors.[49]

Signs and Symptoms of Low T and Hypogonadism

The determination of clinical hypogonadism is based on a low serum testosterone level coupled with specific signs and symptoms.[13] The signs and symptoms of hypogonadism may be vague[4] or nonspecific and can vary according to age, presence of comorbidities, duration and severity of the testosterone deficiency, and variation in androgen sensitivity.[25] Nonetheless, several main signs and symptoms have been identified, including loss of or reduced libido, reduced physical strength, reduced strength of erections, fatigue, and mood changes[23] (see Table 3). Hypogonadism can also lead to decreased lean body mass, increased body fat, and loss of bone mineral density.[50] Other signs and symptoms, such as hot flushes, slow beard growth, and muscular aches, are noted less often.[4]

Most data do not demonstrate a consistent correlation between testosterone level and mood, although hypogonadism may contribute to depression in some subpopulations of men.[51] In a community-based sample of 3987

Table 3

Signs and Symptoms of Hypogonadism

Decreased energy, sense of well-being, or sense of vitality
Decreased muscle strength and mass
Decreased bone density
Increased fatigue
Depressed mood
Impaired cognition
Anemia
Sexual signs and symptoms: decreased libido, intensity of orgasm, or sexual penile sensation; difficulty achieving orgasm; or erectile dysfunction

Data from Rhoden EL, Morgentaler A. Risks of testosterone-replacement therapy and recommendations for monitoring. N Engl J Med. 2004;350:482-492.

men aged 71 to 89 years, a free testosterone concentration in the lowest quintile was correlated with a higher prevalence of depression that did not seem to be associated with physical comorbidity.[52]

Men with total testosterone levels of <300 ng/dL often develop the signs and symptoms of classic hypogonadism.[4] In a recent cross-sectional study conducted to evaluate the prevalence of clinical hypogonadism based on both symptoms and biochemical assessment of testosterone deficiency in 355 men with type 2 diabetes older than age 30 years, 61 men (17%) had overt hypogonadism, with total testosterone <8 nmol/L, and 89 men (25%) had possible hypogonadism, with total testosterone between 8 and 12 nmol/L.[23]

Physical examination may yield information as to the specific cause of testosterone deficiency and can be especially useful in men with severe hypotestosteronemia.[25] Nonetheless, observable signs and symptoms, such as loss of body hair, dry skin, gynecomastia, and decreased testicular volume, may not always occur simultaneously or with the same intensity, which complicates the diagnosis of testosterone deficiency.[25] Furthermore, the signs and symptoms of low T may mimic those of other conditions, including liver disease, thyroid disease, kidney failure, depression, or emotional distress.[28]

Screening for Low T and Hypogonadism

Three screening instruments—the St Louis University Androgen Deficiency in Aging Males (ADAM) questionnaire, the Aging Male Survey, and the Massachusetts Male Aging Study—have been developed to aid physicians in the diagnosis of hypogonadism.[9,53] A comparison of the questionnaires in 148 men aged 23 to 80 years found that the sensitivity for identifying men with low bioavailable testosterone was 97%, 83%, and 60%, respectively; however, specificity was relatively low in all 3 questionnaires (30%, 39%, and 59%, respectively).[9] Questions used as part of the ADAM questionnaire are shown in Table 4.

Table 4

Questions Used as Part of the St Louis University Androgen Deficiency in Aging Males (ADAM) Questionnaire[a]

1.	Do you have a decrease in libido (sex drive)?
2.	Do you have a lack of energy?
3.	Do you have a decrease in strength and/or endurance?
4.	Have you lost height?
5.	Have you noticed a decreased "enjoyment of life?"
6.	Are you sad and/or grumpy?
7.	Are your erections less strong?
8.	Have you noted a recent deterioration in your ability to play sports?
9.	Are you falling asleep after dinner?
10.	Has there been a recent deterioration in your work performance?

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[a] A positive questionnaire result is defined as a "yes" answer to questions 1 or 7 or any 3 other questions.

ANDROTEST, a structured 12-item interview designed specifically for the screening of hypogonadism in men with sexual dysfunction, has been shown to have a sensitivity and specificity of 68% and 65%, respectively, in identifying low total testosterone (ie, <10.4 nmol/L) and 71% and 65%, respectively, for detecting low free testosterone (ie, <37 pmol/L).[10] Given that erectile dysfunction (ED) occurs more often and has been shown to be more severe in men with diabetes than in those in the general population,[54] ANDROTEST could be a particularly useful screening tool in men with diabetes who have ED. For example, in a cross-sectional study of

Table 5

Testosterone Delivery Systems, a Controlled Substance for Use in Men: Dosage and Cost

Delivery System	Dosage	Monthly Cost
Methyltestosterone	10 to 50 mg/d orally	$98
Fluoxymesterone	5 to 20 mg/d orally	5 mg/d: $53 20 mg/d: $214
Buccal testosterone	30 mg twice daily applied to gums	$190
Nonscrotal testosterone patch	Applied to skin once daily	$96
Scrotal patch	Applied to shaved scrotum once daily	$115
Testosterone cypionate	50 to 400 mg intramuscularly every 2 to 4 weeks	$23 per injection
Testosterone enanthate	50 to 400 mg intramuscularly every 2 to 4 weeks	$28 per injection
Testosterone 1% gel	5 g once per day applied topically	$209
Testosterone pellets	150 to 450 mg implanted subcutaneously every 3 to 6 months	Varies

198 men with type 2 diabetes, ED was associated with low bioavailable and free testosterone levels, age, visceral adiposity, and hypertension.[54] A study of 1246 men attending an outpatient ED clinic reported that diabetes associated with hypogonadism could potentially exacerbate sexual dysfunction through decreased mood and libido and compromised penile vascular reactivity.[55]

Several sets of guidelines are also available to aid physicians in the diagnosis and treatment of low T and hypogonadism, including those of the American Association of Clinical Endocrinologists,[11] the Endocrine Society,[8] and the International Society of Andrology, International Society for the Study of the Aging Male, and European Association of Urology.[12] In addition, the Hormone Foundation has recently developed guidelines for patients that serve to explain the procedures involved in the diagnosis of low T as well as the indications for and therapeutic goals of testosterone replacement therapy.[56]

Testosterone Replacement Therapy

The primary goals of testosterone replacement therapy are to restore physiologic testosterone levels and to reduce the symptoms of hypogonadism[4] with a minimum of side effects and a convenient delivery route.[19] The therapeutic goals of testosterone therapy are to improve and maintain masculine characteristics and erections; improve libido, muscle mass and strength, and bone mineral density; and increase energy and well-being.[56]

Several forms of testosterone replacement therapy are available for use in the United States, including injectable, oral, buccal, and transdermal preparations, which are controlled substances.[13] Testosterone pellets are also available but have not been evaluated as thoroughly as the other formulations[18] and are not popular[24] (see Table 5).

The various testosterone formulations differ in terms of ease of administration, patient preference, potential risks, and safety profiles.[13] In general, consistent blood levels of testosterone are not usually attained with oral administration due to first-pass metabolism by the liver; however, depot testosterone via injectable, transbuccal, or transdermal formulations provides sustained release of testosterone into the systemic circulation.[14]

Testosterone Injections

Testosterone injections are usually administered at a dose of 100 mg per week or 200 to 300 mg every 2 to 3 weeks.[13] Serum testosterone levels peak 2 to 5 days after injection and usually return to baseline 10 to 14 days after injection.[13] Disadvantages of this delivery mode include

injection pain, soreness, bruising, erythema, swelling, nodules, or furuncles and the inconvenience of frequent office visits.[13] Patients may also experience a "roller coaster" effect due to fluctuating testosterone levels (ie, alternating symptomatic benefit and return to baseline symptoms).[13] In addition, the risk of erythrocytosis seems to be higher with testosterone injections than topical formulations.[13,21] Advantages of injection therapy include high peak serum testosterone levels and low cost.[13]

Oral and Buccal Testosterone Preparations

Oral testosterone preparations, such as methyltestosterone and fluoxymesterone, are rarely prescribed in the United States because of the potential for adverse effects, mainly hepatotoxicity.[4,13] Testosterone undecanoate is not associated with appreciable hepatotoxicity but is not available in the United States.[13]

A buccal tablet applied twice daily to the upper gum above the lateral incisors[57] has been shown to be effective in achieving testosterone levels in the normal range.[14] Buccal tablets may cause gum irritation or taste alteration.[24]

Transdermal Testosterone

Transdermal testosterone formulations, which are available as scrotal and nonscrotal skin patches and gel preparations, are designed to deliver 5 to 10 mg of testosterone per day.[13] Nonscrotal skin patches can be worn on the abdomen, back, thighs, or upper arm.[58] Gels are usually applied to the shoulders and upper arms[59,60] and/or abdomen.[59]

The main advantages of transdermal delivery include the maintenance of fairly uniform serum testosterone levels and ease of once-daily application[13]; however, the value of this mode of testosterone is reduced in some men because of inadequate transdermal absorption.[13] Some men complain that the nonscrotal skin patch is large, may be visible through shirts, and can be "noisy" with movement.[14] Skin irritations (mostly erythema or pruritus) are frequently reported with testosterone patch usage (up to 66% of patients) but are less common with gel usage (5% of patients)[13]; however, waiting for the gel to dry before dressing is an issue in some men[14] (see Table 6).

Of interest, the 6-month, multicenter, multinational, noninterventional, observational Energy, Sexual Desire and Body Proportions with AndroGel Testosterone study (now in the planning stage) will investigate the safety and efficacy of testosterone gel therapy in 1700 to 2400 men with newly diagnosed hypogonadism who are treated in a usual daily clinical practice setting rather than a formal clinical trial environment.[43]

Emerging Technologies in Testosterone Replacement Therapy

At present, several new testosterone replacement products are in the research and development stage. Emerging technologies include sublingual tablets, nasal and pulmonary delivery methods, and topical aerosols.[19]

Contraindications to Testosterone Replacement Therapy

The use of testosterone replacement therapy in men with age-related hypogonadism or hypogonadism associated with systemic illnesses (eg, diabetes, HIV, cancer, and chronic obstructive pulmonary disease) remains controversial.[50] Indeed, more research studies are needed to determine the precise mechanisms that exist between hypogonadism and systemic diseases, as well as the long-term effect of testosterone replacement on such diseases.[50]

Testosterone acts on a wide range of tissues and organs (eg, prostate, testes, breast, skin, and cardiovascular and respiratory systems)[13] that may be particularly susceptible to the potential adverse effects associated with testosterone replacement therapy[13] (see Table 7). Investigations suggest, however, that many adverse effects are infrequent or rare and that baseline assessment and monitoring can reduce others.[14]

The main contraindication to testosterone replacement therapy is suspected or known prostate cancer.[4,14] To date, no clear evidence supports the claim that testosterone replacement therapy increases the risk of prostate cancer; however, no adequately powered studies have been performed to dispute the claim.[14] In fact, data compiled from several published prospective studies in 461 men with hypogonadism of varying causes and degrees who received testosterone replacement therapy and were followed for 6 to 36 months showed that prostate cancer prevalence was 1.1%, a rate similar to that found in the general population.[13] In addition, numerous investigations have failed to show increased voiding symptoms attributable to benign prostatic hyperplasia in men receiving testosterone replacement therapy, and urinary retention has not been observed more often in men receiving therapy than in those receiving placebo.[13]

Table 6

Transdermal Testosterone Replacement Formulations, a Controlled Substance

Formulation	Advantages	Disadvantages
Gel (hydroalcoholic preparation)	No injections Good clinical response Circadian variation is mimicked Reliable delivery No visible patch Gel dries rapidly	Expensive Potential of transferring testosterone to female partner
Scrotal patch (drug-in-adhesive matrix)	No injections Good clinical response Circadian variation is mimicked	Requires shaving of scrotal area Requires adequate scrotal area Irritation is possible Adhesion problems are possible Increases dihydrotestosterone levels
Nonscrotal patch (liquid reservoir system)	No injections Good clinical response Circadian variation is mimicked Shaving of scrotal area is unnecessary Normal level of dihydrotestosterone is maintained	High likelihood of local skin reactions

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Testosterone replacement therapy is also contraindicated in men with breast cancer.[4,14] Of interest, a recently published case study claims to be the first reported incidence of breast cancer manifesting after a short duration of testosterone replacement therapy.[61] The patient—a 61-year-old man with a 4-year history of erectile dysfunction (ED) and reduced libido and no abnormalities detected on breast examination at baseline—discovered a lump in his right breast 5 weeks after initiation of testosterone gel.[61] Biopsy of the lesion revealed breast cancer, and further pathologic examination showed estrogen receptor–positive invasive carcinoma without nodal involvement.[61] The clinicians involved in this case recommend appropriate patient counseling regarding the risk of breast cancer during testosterone replacement therapy, as well as self-monitoring and clinical examination of the breasts.[61]

Testosterone replacement therapy impairs spermatogenesis and thus should be administered with caution in men with fertility concerns.[4] In addition, men should be advised that testicular size may decrease and testicular consistency may change during testosterone replacement therapy.[13]

Sleep apnea may be exacerbated or develop in men receiving testosterone replacement therapy, usually in those receiving higher doses of parenteral testosterone in whom other risk factors for sleep apnea have been identified.[13] Testosterone replacement likely contributes to sleep-disordered breathing by central mechanisms (not anatomical changes), given that upper airway size is not affected by treatment.[13]

Social or mood disorders are considered to be a relative contraindication to testosterone replacement therapy.[4] Increased body hair, flushing, acne, and oily skin have been reported but are usually thought to be only minor inconveniences.[13] Fluid retention is usually mild and uncommon, but testosterone replacement therapy should be used with caution in men with renal insufficiency or congestive heart failure; reports of hypertension are rare.[13] Acceleration of male-pattern baldness with testosterone replacement therapy has not been adequately studied.[13] Few men receiving treatment report breast swelling and tenderness.[13]

Table 7

Potential Side Effects of Testosterone Replacement Therapy

Potential Risk	Current Evidence
Cardiovascular disease	Possible benefit or neutral
Lipid changes	Usually no change with physiologic testosterone replacement
Erythrocytosis	Risk varies according to method of delivery
	Greater risk with supraphysiologic testosterone levels
	Requires monitoring
Fluid retention	Rarely clinically significant
Benign prostatic hyperplasia	Rarely clinically significant
Prostate cancer	Controversial
	Requires long-term monitoring
Hepatotoxicity	Oral agents only
Sleep apnea	Infrequent
Gynecomastia	Rare and generally reversible
Skin reactions	High incidence with transdermal patch
	Low incidence with gel
	Rare with injections
Acne or oily skin	Infrequent
Testicular atrophy or infertility	Common (particularly in young men)
	Generally reversible on treatment cessation

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Monitoring of Testosterone Replacement Therapy

Prior to initiating testosterone replacement therapy, clinicians should perform blood tests to measure prostate-specific antigen (PSA), hemoglobin, and hematocrit levels; a digital rectal examination (DRE) of the prostate should also be performed.[13] Determination of PSA combined with DRE has been found to have a positive predictive value of 49%[15]; in men with PSA >4 ng/mL or abnormal DRE, a negative result on prostate biopsy should be documented prior to initiation of testosterone replacement therapy.[13] Voiding symptoms and history of sleep apnea should be determined.[13] Assessment of lipids is optional.[13]

Evaluation of treatment effectiveness should take place 1 to 2 months after initiation of testosterone replacement therapy.[13] At that time, clinicians can consider dose escalation in patients with inadequate clinical response correlated with suboptimal testosterone levels.[13] Follow-up testing of PSA, DRE, hemoglobin, and hematocrit should be performed every 3 months during the first year of testosterone replacement therapy and annually thereafter.[14] Each visit should include an evaluation of symptomatic response to treatment, voiding symptoms, and sleep apnea.[13] Monitoring of behavior patterns and mood is also warranted.[15]

Agreement regarding the target level of testosterone replacement therapy is lacking, but many clinicians attempt to achieve mid-normal to upper-normal levels to maximize response to treatment.[13] Treatment that increases levels above the physiologic range is not encouraged, although clinicians should recognize that peak serum testosterone levels usually increase transiently above upper-normal levels with a standard dose of injection therapy.[13]

Dose adjustment is unnecessary in a patient with an adequate clinical response to testosterone replacement therapy, even if testosterone levels are in the low-normal range.[13] Conversely, the testosterone dosage should be increased in a patient with a suboptimal clinical response and testosterone levels in the low-normal range.[13] In men who do not attain adequate serum testosterone levels after receiving the maximum recommended dose of transdermal therapy, injection therapy may be warranted.[13] Consideration of dose reduction or treatment cessation in men with elevated hematocrit should be based on severity.[15]

Potential Barriers to Testosterone Replacement Therapy

Several barriers have been identified that could prevent the appropriate screening, diagnosis, and treatment of low T in men with diabetes. A lack of communication between clinicians and patients is a critical impediment

to optimal care.[6] For example, some clinicians may be reluctant to address the topic of sexual health,[62] and patients may be too embarrassed to initiate the conversation.[6] Female clinicians may be uncomfortable discussing all aspects of sexual health with male patients.[6] The lack of adequate culture-specific resources and appropriate assessment instruments may complicate effective communication.[6]

The primary considerations in diabetes care usually include the monitoring of at-risk systems (eg, kidney, eyes, and vasculature), blood glucose, diet, and exercise, with little time left for a discussion of sexual health[41]; furthermore, diabetes education programs are structured to address similar topics.[6] Many of the symptoms of low T are symptoms of other conditions, which complicates the diagnostic process.[6] For example, patients with systemic diseases, such as diabetes, may assume that signs of sexual dysfunction are caused by the underlying illness rather than low T.[14] In addition, signals offered by patients may go unnoticed because of a lack of clinician awareness.[6]

Some clinicians may attempt to evaluate sexual health by inquiring about ED but do not ask specific questions about other parameters of sexual health or screen for low T.[6] Importantly, diagnosing low T in men with diabetes may require nonstandardized testing that differs from that in men without diabetes.[41] Once diagnosed, a patient with low T could potentially go untreated because of clinician reluctance to prescribe testosterone replacement therapy for fear of adverse effects.[6]

A study analyzing physician variation in diagnosing and treating testosterone deficiency in different parts of the world (ie, Germany, Spain, United Kingdom, Brazil, Saudi Arabia, and South Korea) concluded that more education is required regarding the diagnosis of testosterone deficiency, the relative safety of testosterone treatment, and the role of testosterone in ED.[20] The investigators found that about 68% of physicians associated the use of testosterone therapy with risks more than benefits and that about 35% of men with hypogonadism do not receive testosterone treatment.[20] In addition, between 18% and 29% of men with ED were found to have testosterone deficiency, which was not always diagnosed and treated.[20]

The Effects of Testosterone Replacement Therapy

Data are available on the potential advantages of testosterone replacement therapy on bones, muscles, erythropoiesis and anemia, libido, mood and cognition, penile erection, cholesterol, fasting blood glucose, glycated hemoglobin, insulin resistance,[16] visceral adiposity,[17] and quality of life.[18]

A 7-month double-blind, placebo-controlled crossover study in 24 hypogonadal men with type 2 diabetes aged 30 years and older found that intramuscular testosterone reduced insulin resistance, visceral adiposity, and total cholesterol and improved glycemic control.[17] Data from a study in 108 men aged 65 years and older showed that use of a testosterone patch to increase serum testosterone concentrations to the midnormal range for young men increased lumbar spine bone density in men with low baseline testosterone levels (ie, 200 ng/dL).[63] Small studies have shown that testosterone administration increases fat-free mass,[64] muscle size,[64] and bone mineral density[65] in hypogonadal men.

In a randomized placebo-controlled study in 406 men with hypogonadism aged 20 to 80 years, treatment with testosterone gel (100 mg) versus placebo for 90 days significantly improved sexual desire, motivation, performance, and the number of spontaneous erections. Furthermore, testosterone gel (50 and 100 mg) significantly reduced fat percentage and fat mass compared with placebo.[22,66]

In contrast to data demonstrating the favorable effects of testosterone replacement therapy, a 2-year study in 55 elderly men with relative testosterone deficiency found that use of a testosterone patch (5 mg/day) did not improve carbohydrate tolerance or alter insulin secretion, insulin action, glucose effectiveness, hepatic insulin clearance, or the pattern of postprandial glucose metabolism.[67]

Communicating With Patients About Low T, Sexual Health, and Diabetes

Sexual health may be a window into men's health[68]; thus, more effective communication strategies are needed between clinicians and men with diabetes to ensure that sexual health topics are adequately addressed.[6] The appropriate screening, diagnosis, and follow-up of men expressing sexual problems could be beneficial in the identification and management of other conditions, including diabetes, hypertension, obesity, and hyperlipidemia.[68]

Several approaches have been identified that may serve to improve clinician-patient interactions. First, clinicians must be sufficiently comfortable with their own sexuality

to display an appropriate degree of confidence when asking questions that may be perceived as being personal or embarrassing.[6] If the clinician displays a sense of comfort or confidence, the patient is likely to be more amenable to an open discussion of sexual issues. Second, the clinician must be cognizant of subtle verbal, nonverbal, and clinical assessment cues that could be suggestive of sexual health problems.[6] For example, a question such as, "Does diabetes affect a man's overall well-being or nature?" could be a sign that a man is suffering from loss of libido or is having difficulty achieving or maintaining an erection.[6] Recognizing the importance of such a cue could potentially enable an investigation of other components of the patient's sexual health. Third, clinicians should consider including the patient's partner in conversations about sexual health to facilitate the discussion of sexual dysfunction.[6] Individualizing conversations about sexual health may aid in normalizing a patient's situation and thereby open potentially important channels of communication.[6] Finally, communication with men who have low T should be culturally appropriate to facilitate individualized care in a fast-paced health care setting.[69]

In discussing testosterone replacement therapy, the clinician should appreciate that most men with diabetes who have low T are middle-aged or older and therefore may not have been sexually active for many years.[6] Patients should be counseled that achieving an erection or reaching orgasm may take longer or require more foreplay than at a younger age.[6] If expectations are not age appropriate, a patient may conclude that testosterone replacement therapy has failed, which could promote noncompliance and thus reduce effectiveness.[6] Candid discussions are critical for optimal treatment outcome.[6]

Clinicians must also ensure that patient expectations are realistic regarding the potential benefits of testosterone replacement therapy. The clinician should therefore explain that the rapid improvement in sexual health that often occurs in the early weeks of treatment may plateau when the maintenance phase is reached.[6] During the maintenance phase, some patients may benefit from an added reminder that testosterone replacement therapy will not revive the sexuality of youth and that organ damage caused by diabetes may affect sexual performance.[6] Patient grief based on these realities is a normal response that should be allowed to unfold.[6] The implementation of strategies, such as maintaining a healthy diet, establishing a regular exercise program, and seeking medical attention for psychological conditions, may also be beneficial.[28]

The Role of the Diabetes Educator in a Multidisciplinary Team

Diabetes is a complex chronic disease that requires the skills of a multidisciplinary team of health care professionals for optimal management.[69] The multidisciplinary team may consist of a primary care physician; endocrinologist; diabetes educator, registered nurse, nurse practitioner, or physician assistant; registered dietitian; ophthalmologist or optometrist; social worker, psychologist, psychiatrist, or marriage and family therapist; podiatrist; dentist; and exercise physiologist.[70]

Diabetes educators must be proficient in all areas of diabetes care, including the clinical assessment of complications and comorbidities,[69] and thus can facilitate the identification of men with low T or hypogonadism and initiate the referral process for further assessment and management.[6] The diabetes educator is also in an ideal position to initiate patient conversations about sexual health problems and potential treatment options.[6] Furthermore, frank dialogues between diabetes educator and patient prior to initiation of testosterone replacement therapy may help to eliminate surprises and unrealistic expectations, thereby potentially increasing compliance and treatment outcome.[6] Diabetes educators can also serve to increase awareness of low T and hypogonadism among health care providers.[6] At present, professional education in the identification of men with low T is urgently needed in a wide range of specialties, including primary care, endocrinology, urology, orthopedics, psychiatry, cardiology, and geriatrics.[14]

Patient Education and Public Awareness of Diabetes and Low T

Most diabetes education programs are structured and delivered in a way that does not facilitate adequately addressing sexual issues.[6] As in office visits, diabetes care topics usually include the monitoring of blood glucose and at-risk body systems[41] but not sexual health or low T.[6] In that regard, relevant continuing education programs for diabetes health care providers and diabetes educators are needed to facilitate the proper management of patient sexual health concerns.[62]

Identifying and implementing effective strategies to aid in increasing public awareness about the link between

diabetes and low T should be a key priority. First, relevant print materials made available in provider or educator waiting rooms may encourage patients to initiate a conversation about sexual health and/or respond to provider questions about the signs and symptoms of low T.[6] Second, the creation of interactive, educational Web sites specifically targeting men with diabetes could facilitate the delivery of accurate information on various aspects of sexual health to a large audience.[6] Finally, educational efforts should attempt to dispel the misconception that ED is the only symptom of sexual dysfunction by providing a complete picture of sexual health parameters.[6]

Conclusions

Many men with diabetes who have low T remain undiagnosed and untreated because of a variety of barriers, including lack of patient-provider communication; lack of patient awareness; patient embarrassment; inadequate assessment tool or provider knowledge; personal, cultural, or gender issues; a focus on acute care; or the current structure of diabetes education programs.[6] The elimination of such barriers is central to the goal of providing effective comprehensive care to men with diabetes and is attainable through the implementation of properly structured educational programs targeting clinicians, patients, and the general public.[6]

Testosterone therapy may be a viable option in some men with diabetes and low T, but clinicians must be aware of contraindications to therapy,[4,14] implement appropriate monitoring procedures,[13-15] and ensure that patient expectations are realistic regarding treatment outcome.[6] Furthermore, current testosterone preparations differ in terms of ease of administration, patient preference, potential risks, and safety profiles[13]; thus, individualized treatment is warranted to maximize outcome.

Diabetes educators are ideally positioned to take the lead in screening for low T, providing sexual health information to patients, and increasing clinician awareness of the need to address men's sexual health and implement appropriate strategies; however, the current shortage of diabetes educators must be addressed and rectified.[6] The development of relevant continuing education programs for clinicians[62] and more accurate assessment instruments is needed to facilitate the screening of low T and hypogonadism, as well as general management of patient sexual health concerns.[6] Increasing public awareness through print and online materials about sexual dysfunction, misconceptions about ED, and the link between diabetes and low T could enhance clinician-patient communication.[6] The coordinated efforts of a multidisciplinary team committed to individualized treatment should be encouraged and implemented in men with diabetes and low T.[6]

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