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First REPORT®

The Therapeutic Challenges of Hypogonadism and its Comorbidities

A review of current management of hypogonadism, the comorbidities associated with the disease, and the benefits and risks of treatment.

Sponsored by the Ernest Mario School of Pharmacy
at Rutgers, The State University of New Jersey

March 2006

CPE ACCREDITATION

This activity is approved for one (1) hour credit (0.1 CEUs) and is cosponsored by the Ernest Mario School of Pharmacy at Rutgers, The State University of New Jersey, who is approved by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education.

Credits are available until the expiration date of March 1, 2007. ACPE Program # 038-999-06-001-H01.

This continuing education activity was reviewed by Reza Ghavamian, MD, Associate Professor, Department of Urology, Montefiore Medical Center, Albert Einstein College of Medicine.

STATEMENT OF NEED

Hypogonadism, a condition that affects approximately 20% of men older than 60 years of age, is only treated in 5% of cases. Affecting several aspects of a patient's health, hypogonadism is associated with a variety of comorbidities. In order to reduce the issues related to these comorbidities, recognition of the prevalence of this condition and the importance of effective treatment are necessary.

TARGET AUDIENCE

This educational activity is designed for pharmacists within managed markets.

LEARNING OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- Describe the prevalence of and treatment options for hypogonadism
- Outline the benefits and risks involved in the treatment of hypogonadism
- Identify the comorbidities of hypogonadism

Release Date: March 1, 2006; Expiration Date: March 1, 2007

There is no fee associated with this activity.

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DISCLOSURE INFORMATION

In accordance with the disclosure policy of the Ernest Mario School of Pharmacy at Rutgers, the State University of New Jersey, faculty members are asked to provide information about their affiliation with any organization that may have interests related to the content of this activity.

The faculty disclosed the following:

Mr. Calabrese, Dr. Ghavamian, Dr. Karpman, and Dr. Williams have disclosed they have no actual or potential conflicts of interest in relation to this program.

Dr. Lipshultz: Speaker with honorarium—Auxillium, Solvay Pharmaceuticals

Dr. Morgentaler: Consultant—Auxillium, Solvay Pharmaceuticals; Speaker with honorarium—Auxillium, Solvay Pharmaceuticals

Mr. Calabrese and Drs. Ghavamian, Lipshultz, Karpman, and Williams do not discuss unlabeled/investigational use of any commercial products.

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GRANT SUPPORT

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The Therapeutic Challenges of Hypogonadism and its Comorbidities

Hypogonadism refers to any condition resulting from decreased gonadal function, be it endocrine or exocrine. It has also become synonymous with low serum testosterone and can be associated with a variety of symptoms including a decrease in libido, energy, mental activity, bone density, and muscle mass along with an increased body fat percentage.[1]

Hypogonadism is due to derangements of the pituitary-hypogonadal axis (HPA) and can be classified as primary, secondary, or a combination.[1] Primary hypogonadism refers to failure of the testicles to produce testosterone despite an adequate stimulus from the pituitary gland and is characterized by a low testosterone level, elevated follicle stimulating hormone (FSH) and luteinizing hormone (LH), and impaired spermatogenesis. Secondary hypogonadism is caused by failure of the hypothalamus or pituitary gland to produce an adequate stimulus for testosterone production and is characterized by low testosterone, low or normal FSH/LH, and impaired spermatogenesis.

Testosterone is important in maintaining normal sexual and reproductive function, skeletal growth, and muscle development. It is converted to dihydrotestosterone (DHT), which is important for facial/body hair growth, acne, and prostate development. Testosterone can also be converted by aromatase to estradiol (E2), which plays a role in bone formation and breast tissue development and is important for negative feedback regulation of several central endocrine processes.

According to the 2nd Andropause Consensus Panel, a total testosterone level of less than 200 ng/dL is diagnostic of hypogonadism.[2] When the level is between 200 and 400 ng/dL, clinical considerations and symptomotology as well as a free testosterone should be considered prior to starting therapy. A level greater than 400 ng/dL usually excludes hypogonadism from the diagnosis.

PREVALENCE AND ASSOCIATED COMORBIDITIES

Hypogonadism affects 4% to 5% of the general male population and approximately 20% of men older than 60 years of age.[3-5] A man's total testosterone diminishes by 115 ng/dL per decade after his fifth decade of life. Despite the presumed prevalence of this disease in the United States, only 5% of hypogonadal men are currently receiving treatment, according to the Food and Drug Administration.[6]

There are several concomitant illnesses and conditions, as well as several medications that have been associated with hypogonadism **(Table 1)**. This *First Report* will focus on the most commonly encountered comorbidities seen in a general medical practice, such as end-stage renal disease (ESRD), obesity, diabetes mellitus, and the human immunodeficiency virus (HIV). Additionally, hypogonadism is associated with osteoporosis as a risk factor for the degenerative bone condition.

ESRD is the end result of chronic renal failure, which is characterized by marked HPA dysfunction that is reversed by renal transplantation but not hemodialysis.[7] Approximately half of all males with ESRD complain of erectile dysfunction and decreased libido.[8] These patients characteristically have low levels of free and total testosterone along with elevated levels of LH, FSH, and estradiol demonstrating signs of both primary and secondary hypogonadism.[9] Testosterone replacement has been shown to benefit libido, bone mineral density (BMD), and red cell mass, all commonly related problems with ESRD. A minimal improvement in erectile dysfunction is seen with testosterone administration in ESRD patients.[10] Parenthetically, we do not see elimination of testosterone with hemodialysis.[11]

It has been reported that approximately 60% of Americans are overweight and one third are considered obese.[12] Obesity is associated with decreased lean muscle mass and increased visceral and peripheral fat. Testosterone is converted into estradiol in fat, causing further changes in testosterone and estradiol ratios. Hypogonadism is also associated with abnormalities in cortisol secretion which causes truncal deposition of fat, further compounding the problem of obesity and complicating weight loss.[13] Treatment with testosterone has been

Table 1. General Medical Disorders Associated with Hypoganadism

Amyloidosis	COPD	Obesity
ESRD	Diabetes mellitus	Rheumatoid arthritis
Chronic infections	Hemochromatosis	Sickle cell disease
Cirrhosis	HIV	

COPD = chronic obstructive pulmonary disease; ESRD = end-stage renal disease; HIV = human immunodeficiency virus.

shown to increase lean body muscle mass, decrease percent fat composition, increase insulin sensitivity, decrease fasting blood glucose, improve plasma cholesterol levels, and decrease diastolic blood pressure.

Another common disease in our society is diabetes. Twenty percent of diabetic men have a low serum testosterone level and 55% are reported having a low serum free testosterone level.[14] The problem is compounded with aging, with 36% of diabetic men older than 70 years of age having low testosterone levels. The association between hypogonadism and the development of insulin resistance is supported by epidemiologic studies showing a 2.7 times greater risk of developing diabetes in this population.[15] Further evidence from Finland has shown that the risk of metabolic syndrome (the presence of 2 or more metabolic risk factors such as abdominal obesity, elevated blood pressure, dyslipidemia and insulin resistance) is 2.5 times greater in hypogonadal men with total testosterone levels in the lowest quartile.[16] Testosterone replacement has been shown to decrease blood glucose values and mean glycated hemoglobin (HbA1C).[17]

Men infected with HIV represent a growing population of men diagnosed with hypogonadism. Approximately 20% to 40% of HIV positive men and 50% of men with acquired immune deficiency syndrome (AIDS) are diagnosed with hypogonadism.[18] The etiology of hypogonadism in this subset of patients is multifactorial and related to direct viral infection of the testes causing testicular failure in some instances. Diminished hypothalamic pituitary function along with the side effects from antiretroviral medications are also implicated in hypogonadism in these patients. Double-blind, placebo-controlled studies have demonstrated the effectiveness of treatment of hypogonadal symptoms in HIV- and AIDS-infected men.[19]

A list of commonly prescribed drugs that have been shown to interfere with normal testosterone production and bioavailability is included in Table 2. There are 3 predominant mechanisms by which these drugs can lead to hypogonadism: by blocking testosterone production, reducing gonadotropin-releasing hormone secretions, and blocking androgen receptors. Fortunately, discontinuation of the offending drug and allowing for an adequate recuperation period is all that is required for effective treatment.

Since hypogonadism is the most common secondary cause of osteoporosis, TRT may improve bone density to help prevent this disease and related complications.[20] Studies have shown a correlation between BMD and hypogonadism through an increased risk of hip fracture in hypogonadism, with BMD being directly related to bioavailable testosterone rather than total testosterone.[20] Additionally, long-term prospective and retrospective studies have shown that TRT therapy improves BMD in the lumbar spine and femoral neck.[20]

DIAGNOSIS OF HYPOGONADISM

The development of a validated questionnaire assessing symptoms has facilitated the diagnosis of hypogonadism.[21] A complete physical examination focusing on virilizing characteristics, the genitalia, and a digital rectal examination should be completed. Identifying patients who have signs and symptoms suggestive of hypogonadism should be followed by confirmatory blood tests demonstrating a low total or free testosterone level. Serological tests are necessary to confirm the diagnosis of hypogonadism.

THERAPEUTIC BENEFITS AND MODES OF DELIVERY

The goal of testosterone replacement therapy (TRT) is to provide and maintain normal levels of testosterone as well as its metabolites DHT and E2, thus providing positive effects on sexual, physical, and psychological functions.[22] There are several forms of TRT available for the treatment of hypogonadism—intramuscular (IM), oral, transdermal, gel, and buccal system.

There are 2 available injectable forms of long-acting IM testosterone, testosterone enanthate and cypionate. Serum levels are not maintained beyond 2 to 3 weeks even with higher than normal injection doses (>100-200mg per week), necessitating repeat injection every 2 to 3 weeks. DHT levels are usually normal; estradiol levels can be high, causing gynecomastia. A significant advantage to this form of therapy is the relatively low cost of treatment (~ $12/injection). Pain and anxiety about injections, lack of a circadian rhythm, and large serum variations between doses are some of the disadvantages.

Oral administration provides an easier route of administration in contrast to IM testosterone, but the tablet must be taken 3 to 4 times daily. Moreover, erratic absorption and no circadian variation occur during oral therapy. Preparations for oral administration include methyltestosterone, oxymetholone, and fluoxymesterone. These derivatives minimize first-pass hepatic metabolism. It is difficult to achieve therapeutic levels of testosterone after oral administration due to the extensive metabolism of testosterone in the gastrointestinal tract and liver, and its short terminal half-life (~100 minutes).

Transdermal patches are able to restore testosterone to normal levels, and peak testosterone levels can be achieved in the morning, simulating the normal diurnal variation. The greatest disadvantage of patch therapy is the high rate of skin reactions (67%) reported at the patch application site.[23] Pretreatment with a mild topical steroid cream or a diphenhydramine spray as well as varying the application site has been shown to minimize this problem.

Recently, testosterone therapy in a gel formulation has been introduced. The product has been shown to cause minimal side effects. Studies looking at the percentage of hypogonadal patients with testosterone levels in the eugonadal range follow-

Table 2. Medications Commonly Associated with Hypoganadism

GnRH agonists/antagonists	Psychotropic drugs
Estrogens	Aldactone
Progestins	Thiazide diuretics
Glucocorticoids	Opiates
Ketoconazole	Anabolic steroids

GnRH = gonadotropin-releasing hormone.

ing gel application is very favorable (89% to 94%) and is sustained during chronic administration (6 months).[24] The disadvantages of transdermal gels are the need for daily application and the risk of transference to other individuals if precautions are not taken. Minimal site reactions are reported.

The newest TRT formulation, the testosterone buccal delivery system, is designed to adhere to the gum surface above the incisor tooth on either side of the mouth. This system provides controlled and sustained release of testosterone, which is delivered through the buccal tissue and not through the saliva or orally. Delivery of testosterone through the buccal mucosa avoids first-pass hepatic metabolism, minimizing hepatic toxicity. The disadvantages include minimal local irritation, a bad taste in the mouth, and poor patient compliance with twice daily dosing.

TREATMENT RISKS

TRT's theoretical risks of polycythemia, sleep apnea, infertility, increased prostate symptoms and prostate cancer, and cardiac disease still concern many healthcare providers and prevent their use of TRT in hypogonadal patients. Although information is available demonstrating an acceptable safety profile for TRT, unequivocal data are still lacking regarding the risks of therapy.

The erythropoietic-stimulating effect of TRT has been well known for many years.[25] Polycythemia is associated with the type of TRT used and has been reported to be as high as 40% in patients using IM injections but rarely with transdermal applications.[26] Predisposed individuals usually manifest polycythemia within 6 months of initiating therapy. TRT requires annual monitoring of patients and discontinuation of therapy when the hematocrit is above 52%.

All forms of testosterone supplementation have a similar effect by lowering the amount of hormones produced from the pituitary and hypothalamus. This, in turn, causes decreased secretion of FSH/LH leading to diminished endogenous testicular function. Testicular atrophy is commonly seen in patients on TRT.

All exogenously administered testosterone acts, likewise, as a male contraceptive by lowering sperm densities to zero.[27] This effect is evident even at minimal doses administered. Endogenous testosterone is essential for sperm production, epididymal maturation, and production of seminal plasma.[28] The common misconception by practitioners is that in hypogonadal patients, placing them on TRT will improve all of these parameters. Despite improvements in serum testosterone levels, TRT has the secondary effect of eliminating FSH stimulation of Sertoli cells necessary to produce sperm. Fortunately, most of these patients with impaired sperm production following TRT will recuperate their testicular size and sperm production within 6 months of discontinuation of therapy.[29]

Painful gynecomastia is a reported side effect of therapy in some patients. This is related to increased estrogen levels due to aromatization of testosterone. Gynecomastia is more commonly encountered in patients using IM therapy because their testosterone levels tend to be higher and, hence, they have higher estradiol levels. Dose titration or treatment with aromatase inhibitors (anastrozole, letrozole) or selective estrogen receptor modulators (tamoxifen) are effective options for reducing this side effect.[30]

Studies evaluating TRT have shown only minimal changes in prostate volume or prostate-specific antigen (PSA) in younger men and only a modest increase (15%) in older men.[31] Clinical trials evaluating TRT have shown no change in objective voiding parameters, such as post-void residual and uroflowmetry, or even in subjective clinical symptoms. The concern over development of *de novo* prostate cancer exists because of the established androgen dependence of this disease demonstrated by Huggins and Hodges in 1941.[32] However, concern that giving TRT to hypogonadal men will increase the risk of developing prostate cancer has not been proven true. Longitudinal studies using frozen sera from men who went on to develop prostate cancer have provided good evidence showing that men with elevated testosterone levels do not have any higher incidence of developing prostate cancer.[33,34]

Rhoden and Morgentaler compared 20 hypogonadal men with prostate intraepithelial neoplasia (PIN) to 55 hypogonadal men without it.[35] Both groups were treated with TRT showing a similar rise in PSA (0.3 ng/mL) and only 1 case of prostate cancer (5%) was detected in the PIN positive group and none in the PIN negative group. This incidence of cancer still represents a much lower incidence of prostate cancer than the expected rate of 25% at 3 years seen in previous evaluations in this high-risk population.

The evidence that men have a greater incidence of coronary artery disease (CAD) than women has suggested that high testosterone levels are associated with an increased risk of CAD. The possible causal role of testosterone in the development of CAD has not been proven, and there are no epidemiologic data, to date, implicating TRT. Studies investigating men with and without CAD have shown that total and free testosterone levels are similar.[36]

In a 2001 study, testosterone improved symptoms of angina and delayed time to ischemic threshold in hypogonadal men with coronary disease. In a recent meta-analysis reviewing 19 studies, the authors found that TRT reduced total cholesterol (-14 mg/dL), low-density lipoprotein (-5 mg/dL), high-density lipoprotein (-4 mg/dL), and triglycerides (-1mg/dL).[37] Collectively, these data would suggest even a protective role of testosterone in men.

CONCLUSION

A better understanding of the significant role hypogonadism plays in ageing males as well as in a variety of other medical conditions is growing. Hypogonadism is associated with a wide range of symptoms and comorbidities that are exacerbated by the typical age of hypogonadism patients. Without awareness or appropriate diagnostic testing, hypogonadism—and the comorbidities associated with the disorder—will remain underdiagnosed and undertreated in our male population. ■

Complete list of references available through Princeton Media Associates, LLC.. Call 609-371-1137 or e-mail info@princetoncme.com

Managed Care Commentary

David Calabrese, RPh, MHP, MedMetrics Health Partners, Northeastern University Bouvé College of Pharmacy and Allied Health Sciences

While it is not uncommon for many managed care organizations (MCOs) to focus more considerable resources and attention toward women's health issues, the appropriate diagnosis and clinical management of male-specific disorders such as hypogonadism should probably take equal precedent. It is clear, given the symptomatology of the hypogonadal male, that a failure to adequately diagnose and treat these individuals can predispose them to other more significant issues such as mood disorders, psychosocial problems, decreased productivity, and other potential clinical sequelae such as increased future risk of osteoporotic fracture.

Given current drug utilization patterns with TRT, the estimated percentage of males currently being actively treated for this disorder remains very low (probably <3% of the male managed care population). Drug utilization patterns however are probably a poor marker of true prevalence, as the likelihood is strong that hypogonadism is both underdiagnosed and undertreated. More than likely, this phenomena results from a general difficulty that males experience in speaking with medical practitioners about the symptoms associated with low testosterone, as well as a lack of patient education and understanding of the condition and its treatment options. As hypogonadism is a disorder that increases with age, many men who experience its symptoms are also not likely to seek treatment assuming that their symptoms are a natural part of the aging process.

The data presented in this *First Report* regarding the number of comorbidities that may be associated with hypogonadism were rather eye-opening. While it was not surprising that this condition may be tied to obesity and diabetes, many of the other comorbidities presented were not conditions many would routinely associate with hypogonadism.

Most MCOs today have embraced the value of appropriate diagnosis and treatment of hypogonadism. This is evident in the fact that most managed care drug formularies today provide a wide array of options in the area of TRT, and many organizations have incorporated into their men's health programming specific educational initiatives designed to bring greater awareness of the condition to its male members.

There are clearly pros and cons with all available TRT methods. In evaluating products for formulary inclusion, it is critical that all key factors discussed in this *First Report* be weighed in the decision-making processes and that a variety of preferred options be available to allow the provider and patient to discuss treatment options and individualize therapy to best suit the specific needs and desires of the given patient. ■

Clinical Commentary

Abraham Morgentaler, MD, Harvard Medical School

The greatest challenge in the diagnosis of hypogonadism is the lack of a clear cut threshold level for any blood test below which hypogonadism can be readily determined. Total testosterone is the most commonly used test, but a substantial portion of it is so tightly bound to sex-hormone binding globulin (SHBG) that it is not biologically active. Since SHBG tends to rise with age, an older man may have a "normal" total testosterone but may be truly hypogonadal, with low levels of bioavailable testosterone. Although some have argued that the free testosterone assays available in most hospital laboratories are suboptimal, my experience is that this surrogate for bioavailable testosterone is very helpful in helping to identify the symptomatic individual with low-normal levels of total testosterone.

TRT OR NO TRT OR WHICH ONE?

Deciding whether to treat this condition is evaluated across several factors, the risk of treatment, the need for treatment, and the choice of therapy. The data regarding the safety of TRT have been reassuring. The most common significant risk is erythrocytosis, affecting less than 5% of men on gel therapy. Concerns regarding an increased risk of prostate cancer have not been supported by the evidence. Similarly, the risk of cardiovascular disease does not appear to be any greater in men receiving testosterone than men who do not. Indeed, men with high testosterone levels appear to be at substantially lower risk of severe atherosclerosis than men with low levels.

As the *First Report* highlighted, hypogonadism is associated with a number of common medical conditions, and how those diseases and the person's quality of life can be negatively affected by low testosterone are infrequently discussed. For example, although it is well recognized that some of men with diabetes suffer from erectile dysfunction, it may be less well known that hypogonadism may affect them as well. In some cases, these men may benefit from TRT for symptoms of diminished libido or fatigue, and may benefit from TRT even if they have already responded to a phosphodiesterase inhibitor for erectile dysfunction.

Determining the most appropriate modality for TRT is based on several factors. Gels are generally the first choice if the patient has insurance coverage, as they provide good serum levels, and are easy to apply. Patches are the preferred modality for some formularies, particularly in the Veterans Administration system, but they are associated with a high rate of bothersome skin reactions. Injections are effective and inexpensive, and are used primarily when cost is an issue, or if inadequate serum testosterone levels have been achieved via transdermal preparations. Finally, although oral forms of testosterone are available in the United States, their use is highly discouraged due to an association with significant liver toxicity. ■

Post-Test

This activity is approved for one (1) hour credit (0.1 CEUs) and is cosponsored by the Ernest Mario School of Pharmacy at Rutgers, The State University of New Jersey, who is approved by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education.

Credits are available until the expiration date of March 1, 2007. ACPE Program # 038-999-06-001-H01.

Participants should select the single most appropriate answer to each of the following questions.

1. Hypogonadism is associated with which of the following symptoms?
   a) Increased muscle mass
   b) Decreased body fat percentage
   c) Decreased libido
   d) None of the above

2. Hypogonadism affects ___% of men over 60 years of age.
   a) 4
   b) 20
   c) 24
   d) 60

3. Patients with ESRD typically present with signs of which type of hypogonadism?
   a) Both primary and secondary
   b) Primary
   c) Secondary
   d) Endocrine

4. TRT has been shown to decrease _____, a benefit to patients with comorbid diabetes.
   a) Blood glucose values and HbA1C
   b) Testosterone
   c) Estradiol
   d) Sleep apnea

5. Hypogonadism in patients with HIV and AIDS is related to:
   a) Antiretroviral therapy
   b) Blocked androgen receptors
   c) Viral infection of the testes
   d) A and C

6. The predominant mechanism by which certain drugs can lead to hypogonadism is by:
   a) Blocking testosterone production
   b) Reducing gonadotropin-releasing hormone secretions
   c) Blocking androgen receptors
   d) All of the above

7. Studies have shown that hypogonadism is related to _____ through an increased risk of hip fracture.
   a) Diabetes
   b) BMD
   c) Metabolic syndrome
   d) Prostate cancer

8. Which of the following is not an available form of TRT?
   a) Buccal system
   b) Transdermal patch
   c) Intravenous
   d) Oral

9. Impaired sperm production due to TRT is often resolved with:
   a) Discontinuation of therapy.
   b) Change in therapy.
   c) Addition of infertility treatment.
   d) There is no way to resolve the impairment.

10. A recent study found that TRT had what effect on CAD?
    a) Increased the risk of CAD
    b) Exacerbated the symptoms of angina
    c) Shortened the time to ischemic threshold
    d) Reduced total cholesterol, high-density and low-density lipoprotein, and triglycerides

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The Ernest Mario School of Pharmacy at Rutgers, the State University of New Jersey would appreciate your comments on the quality of this educational activity. Please answer the following 6 questions—1 through 4 using a 5-point grading system, with 1 being the lowest rating (strongly disagree/poor) and 5 being the highest rating (strongly agree/excellent).

1. Upon completion of this educational activity, the participant was able to:

   Describe the prevalence of and treatment options for hypogonadism

   1 2 3 4 5

   Outline the benefits and risks involved in the treatment of hypogonadism

   1 2 3 4 5

   Identify the comorbidities of hypogonadism

   1 2 3 4 5

2. How current was the information presented in this activity?

   1 2 3 4 5

3. This educational activity was objective, balanced, and free of commercial bias.

   1 2 3 4 5

4. Please indicate your overall evaluation of this activity.

   1 2 3 4 5

5. Do you intend to make changes to your practice as a result of this activity?

   1 2 3 4 5

6. What aspects of this activity were of most interest to you?

   _____

7. Do you have any comments or suggestions for this or future activities?

   _____

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