

Male Hypogonadism in Systemic Disease

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The effect of age on gonadal status has been recognized, but the interaction of systemic illness and androgen deficiency is not as thoroughly understood. Hypogonadism associated with acute and chronic illness is becoming more recognized (Box 1) and can occur as a result of the illness itself or its treatment. Although treating men who have male hypogonadism is standard medical practice, testosterone replacement therapy is still a controversial issue in the context of hypogonadism associated with age or systemic diseases. More studies are needed to delineate the exact mechanisms by which hypogonadism is related to diseases and to determine the long-term effects of testosterone replacement on most systemic illnesses. It is crucial to address these relationships because male hypogonadism may contribute to a reduced quality of life and poorer health outcomes. This article reviews the epidemiology of hypogonadism in common acute and chronic illnesses, the possible mechanisms that cause low testosterone levels (Fig. 1), and the results of replacement studies, if available.

General symptoms of hypogonadism

Hypogonadism is associated with a host of symptoms, including sexual dysfunction, reduced energy, depressed mood, poor concentration and memory, mild anemia, and a diminished sense of well-being [1]. Many of these symptoms are nonspecific and are often present in aging men or in men who have chronic disease. Hypogonadism can also result in decreased lean body mass, loss of bone mineral density, and increased body fat. As an example

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Box 1. Systemic illnesses associated with hypogonadism

- Burn injury
- Stroke
- Traumatic brain injury
- Myocardial infarction
- Respiratory illness
- Sepsis
- Surgical stress
- Cancer
- Chronic opioid exposure
- Chronic renal failure
- Chronic liver disease
- Rheumatoid arthritis
- HIV
- Chronic obstructive pulmonary disease
- Diabetes
- Obesity

of the significance of this observation, changes in body composition have been well studied in HIV disease. Reduced lean body mass is found in AIDS wasting and correlates with increased risk of mortality [2]. Thus, male hypogonadism may explain or worsen many signs and symptoms of men who have systemic diseases. It is therefore crucial to diagnose hypogonadism if it is present in patients suffering from systemic diseases and to determine whether or not testosterone replacement is appropriate for alleviating some of these problems.

Laboratory diagnosis of male hypogonadism in the setting of systemic diseases

The Endocrine Society, in their recently published Clinical Practice Guidelines, recommends that when a patient presents with signs and symptoms suggestive of androgen deficiency, measurement of morning serum total testosterone levels should be performed. A patient who has a total testosterone level below 300 ng/dL is likely to be hypogonadal. In patients who have levels between 200 and 400 ng/dL, the test should be repeated along with measurement of free testosterone. Measurement of free testosterone or sex-hormone-binding globulin (SHBG) levels is helpful in determining bioavailable testosterone because many systemic conditions are associated with changes in SHBG levels. Specifically, increases in SHBG can be detected in hepatic cirrhosis, hyperthyroidism, HIV infection, and anticonvulsant use; reductions in SHBG are noted with moderate obesity, low protein states (nephrotic syndrome), hypothyroidism, hyperinsulinism, and glucocorticoid use.

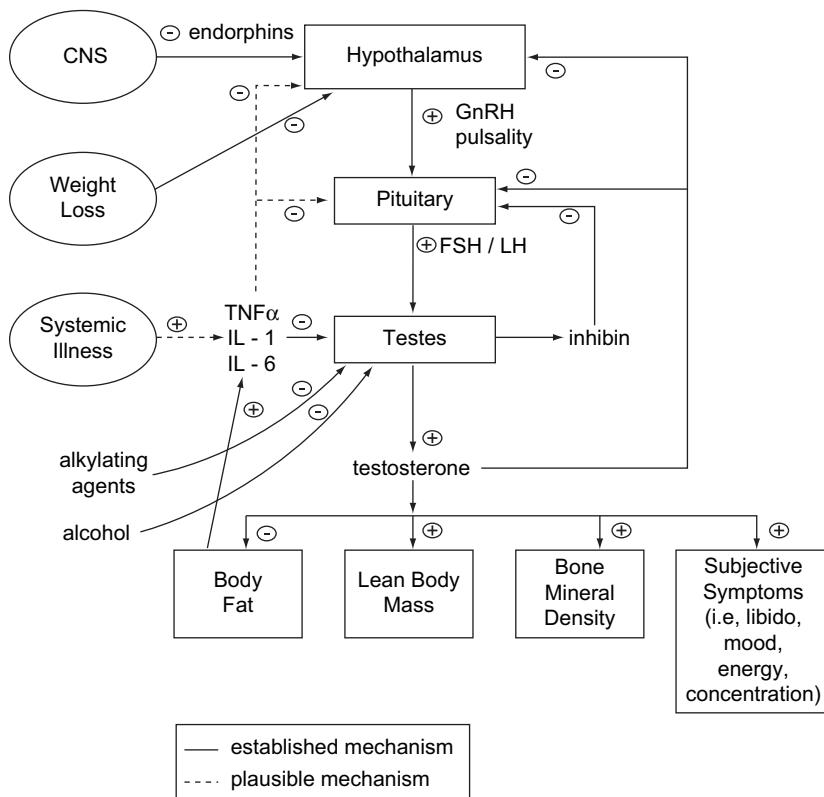


Fig. 1. Mechanism of action of the hypothalamic-pituitary-gonadal axis in systemic disease.

Measurement of leuteinizing hormone (LH) and follicle-stimulating hormone (FSH) is recommended to determine whether androgen deficiency is due to primary testicular failure, in which case the gonadotrophins would be elevated or due to secondary disturbances in the hypothalamus-pituitary-gonadal (HPG) axis, causing low gonadotrophin levels. The two types of hypogonadism can occur together, and this is often the case in many illnesses.

Acute illness

Since the 1970s, hypogonadism has been described in acute illness associated with surgery [3–5], stroke [6], traumatic brain injury [7], myocardial infarction [8], respiratory illness [9], sepsis [10], liver disease [10], and burns [11–13]. In a study of chronically critically ill men requiring mechanical ventilation and intensive nursing care, 96% of patients had bioavailable testosterone levels well below the lower limit of their age range after a median ICU length of stay of 25 days. The bioavailable testosterone values were

approximately $11 \pm 11\%$ of the means for normal men in each decade [14]. As many as 90% of men with total body burns of 15% or greater have been found to have hypogonadism [11]. One report found that 24% of patients who had traumatic brain injury had gonadal dysfunction [7].

Primary and secondary hypogonadism have been reported with parallel changes in bioactive and immunoactive LH and FSH in critically ill patients [8,15], and some researchers have suggested that primary hypogonadism may be present to a greater degree in patients who have more severe illness [9]. Exogenous intravenous gonadotropin-releasing hormone (GnRH) pulses can partially or completely overcome hypogonadotropic hypogonadism, supporting a combined hypothalamic-pituitary-gonadal origin [7,16]. Mean free and total testosterone levels were found to fall by approximately half in men who had myocardial infarction, traumatic brain injury, and elective surgery within 24 hours [17]. Normalization of testosterone levels occurred 2 to 8 months after acute brain injury. FSH and LH levels were lower or unchanged. As evidenced by the significant fall of FSH, LH, and estradiol in predominantly postmenopausal women within 24 to 48 hours after the acute event, central hypogonadism occurs with acute illness in both genders [17]. In vivo results suggest that diminished activity of 17,20-desmolase may be a mechanistic explanation for reduced testosterone production within the testis [10]. SHBG levels remain unchanged [10,17].

In patients who have burns, free and total testosterone levels decline rapidly within 24 hours after injury and reach a nadir on average at day 11 or 12, whereas LH levels may remain unchanged or fall below normal by the fourth day [11,12]. Decreased pulsatility of LH release in burn patients has been found, suggesting a plausible mechanism for central hypogonadism in this condition [13]. Another explanation proposed is reduced biologic activity of LH as determined by bioassay techniques [13]. Inhibition of adrenal and testicular C-19-steroid secretion has been suggested by the finding that serum dehydroepiandrosterone sulfate, dehydroepiandrosterone, androstenedione, and testosterone concentrations fall during the first 4 weeks after burn trauma, whereas serum cortisol and 17-hydroxycorticosteroid levels rise in these studies as well [12].

The degree of hypothalamic-pituitary-gonadal axis suppression is related to the severity of illness in critical care patients. Patients who had more severe illness as described by the APACHE score or burns had significantly more profound declines in testosterone levels than those who had relatively mild or moderate illness [9,11]. Severity of head trauma is correlated to hypogonadism, with patients who had the lowest Glasgow Coma Scale score displaying the lowest levels of baseline and peak FSH and testosterone [7]. Chronically ill patients have a more marked reduction in testosterone levels than acutely ill patients [10]. Mean testosterone level among critically ill patients has also been suggested to be a predictor for mortality because surviving patients have significantly higher testosterone levels than nonsurvivors [10].

There is no established role for treatment of critically ill patients with testosterone outside of research protocols, although promising results have been obtained with the use of testosterone and its analogs in burn injuries. In six men who had total body burns of more than 70%, administration of testosterone enanthate 200 mg/wk intramuscularly for as little as 2 weeks resulted in significantly increased protein synthetic efficiency and only half the protein breakdown [18]. The oral testosterone analog oxandrolone has been found to have comparable results to other anabolic agents, such as human growth hormone, in its ability to decrease daily nitrogen loss while improving healing time [19]. These beneficial effects of oxandrolone (20 mg/d) were reproduced in a randomized, double-blinded, placebo-controlled trial in patients who had 40% to 70% total body surface area burns [20]. Positive effects on body weight and lean mass were retained 6 months after discontinuation of oxandrolone [21]. Another study of oxandrolone in burn patients found significantly decreased lengths of stay, although hepatic transaminases warranted monitoring [22]. Table 1 presents an overview of the efficacy of testosterone treatment of men who have hypogonadism and systemic disease.

Chronic illness

Chronic opioid exposure

Long-acting opiate preparations of methadone, morphine sulfate, oxycodeone, and fentanyl for the treatment of chronic malignant and nonmalignant pain in men commonly result in opioid-induced androgen deficiency [23]. As many as 5 million men who have chronic nonmalignant pain may have androgen deficiency from opioid use in the United States [24]. In outpatient male patients taking sustained-action oral opioids for nonmalignant pain, as many as 87% of men who have normal erectile function before opioid use reported severe erectile dysfunction or diminished libido after use [25]. Hormone levels were lower in opioid users in a dose-dependent pattern. In a case-control study of 40 cancer survivors who had chronic pain, Rajagopal and colleagues [26] found that chronic opioids users had higher levels of hypogonadism and sexual dysfunction compared with control subjects (90% versus 40%). The prevalence of sexual dysfunction on methadone maintenance was reported to be 14% in one study [27]. High-dose methadone can decrease testosterone levels in male heroin addicts, leading to decreased sexual drive and performance [25,28–30]. Buprenorphine seems not to suppress testosterone levels and may be favored in the treatment of heroin addiction to prevent methadone-induced hypogonadism [31].

Suppression of pulsatile GnRH by the hypothalamus secondarily leads to reduced LH by the pituitary and testosterone by the gonad. Naturally occurring opiates (endorphins) may diminish testosterone levels by inhibiting GnRH. Direct suppressive effects on the pituitary and testes have also been proposed [32,33]. The acute decline in LH levels and testosterone can occur as soon as 1 to 2 hours after administration of a subcutaneous

Table 1
Strength of studies that have shown benefit in treatment of hypogonadism in systemic illness

Disease	Intervention	Strength of benefit	Nature of benefit	Study
Burn injury	IM testosterone injection	***	Protein synthetic efficiency	Ferrando et al, 2001 [18]
	Oxandrolone	****	Lean body mass, wound healing	Demling and Orgill, 2000 [20]
Cancer	Testosterone patch	****	Fatigue, activity	Howell et al, 2001 [55]
Chronic opioid exposure	Testosterone patch	****	Sexual function, mood	Daniell et al, 2006 [23]
Diabetes/obesity	IM testosterone injection	****	Glycemic control, obesity	Kapoor et al, 2006 [95]
	Oral testosterone undecanoate	****	Glycemic control, obesity, erectile dysfunction	Boyanov et al, 2003 [96]
HIV	IM testosterone injection	****	Lean body mass, quality of life	Grinspoon et al, 1996 [64]
COPD	IM testosterone injection	***	Lean body mass, bone mineral density	Casaburi et al, 2004 [74]
Chronic liver disease	Testosterone gel	**	Muscle strength, survival	Neff et al, 2004 [82]
Chronic renal failure	Nandrolone decanoate	***	Lean body mass, functionality	Johansen et al, 1999 [88]
Rheumatoid arthritis (no steroids)	Oral testosterone undecanoate	***	RA symptoms, libido	Cutolo et al, 1991 [92]
Rheumatoid arthritis (with steroids)	IM testosterone injection	None	None	Hall et al, 1996 [93]

Relative strength of benefit indicated by number of asterisks (**** = highest). Diabetes and obesity are not formally discussed in this review since they are covered by other authors in this journal.

Abbreviations: COPD, chronic obstructive pulmonary disease; IM, intramuscular; RA, rheumatoid arthritis.

injection of morphine [34]. Opiate antagonists such as naltrexone may partially reverse these effects and may lead to significant elevation in LH levels but no changes in testosterone levels [35]. Tolerance to opiates may develop, and effects on GnRH and gonadotropin secretion may lessen with time [35].

In a recent 24-week, open-label, pilot study of testosterone patch therapy (5 mg/d for the first 12 weeks, 7.5 mg/d for the second 12 weeks) of 16 men who had androgen deficiency from opioid use [23], free testosterone levels significantly increased. At a dose of 7.5 mg/d, sexual function, mood, and depression scores showed significant improvement, and the patches were well tolerated.

Cancer

Testicular dysfunction can be present in cancer patients pre- or post-treatment. In Hodgkin's disease, approximately one third of patients have oligospermia, and up to 70% of men who have Hodgkin's disease have abnormal semen analysis [36–39]. In testicular cancer, over 50% of men have oligospermia before treatment [37,40].

Explanations for the pathophysiology of testicular dysfunction in Hodgkin's disease are lacking, although proposals have included effects on semen quality or immune-mediated effects [41]. FSH levels are lower than normal, suggesting that pre-treatment hypogonadism may be mediated by the pituitary and the gonad in Hodgkin's disease [36]. In testicular cancer, mechanisms may include local tumor effects, elevation of scrotal temperature, alterations in testicular blood flow, testicular fibrosis, or sperm antibodies [42]. Central hypogonadism may be caused by ectopic adrenocorticotropin hormone-producing tumors or by androgen-producing tumors.

Factors affecting impairment and recovery of spermatogenesis after cytotoxic therapy include the agent used, the dose received, and the age of patient or maturation of the testis at the time of insult [43–46]. The germinal epithelium of the adult testis may be more prone to cytotoxic damage than the prepubertal testis [47]. Gonadotoxic agents include cyclophosphamide, chlorambucil, mustine, melphalan, busulfan, carmustine, lomustine, cytarabine, vinblastine, procarbazine, and cisplatin [48]. Irradiation dose similarly affects the speed and extent of recovery in radiation-induced testicular damage [49]. Single-dose irradiation with as low as 0.1 Gy can cause oligospermia, and doses above 0.8 Gy result in azoospermia. Recovery to pre-treatment sperm concentrations can take up to 5 years or more for doses of 4 Gy and above. In contrast to cytotoxic injury, irradiation may more severely affect Leydig cell function in the prepubertal testis [50].

Howell and colleagues [51] found that in their cohort of patients treated with mustine, vinblastine, procarbazine, and prednisolone; chlorambucil, vinblastine, procarbazine, prednisolone, etoposide, vincristine, and doxorubicin hybrid; or high-dose chemotherapy for a variety of hematologic malignancies, one third of patients had evidence of Leydig cell dysfunction, and 90% of patients had germinal epithelial failure. High cumulative doses of cisplatin (>400 mg/m²) in patients who have germ cell tumors of the testis are

associated with significantly lower mean testosterone levels, lower testosterone/SHBG ratios, and higher LH levels compared with similar patients not treated with chemotherapy [52]. In bone marrow transplant recipients presenting with fatigue, diminished libido, and erectile dysfunction, compensated Leydig cell insufficiency (high LH with normal testosterone levels) was predominant [53].

The use of intramuscular testosterone injections of testosterone cypionate (250 mg 4 times weekly) for 6 months and sildenafil in patients who had erectile dysfunction after bone marrow transplant has been reported with favorable results [54]. Howell and colleagues [55] followed a cohort of 35 men who had LH of 8 IU/L or higher and testosterone levels in the lower range of normal or frankly below normal (testosterone less than 20 nmol/L) after cytotoxic chemotherapy for hematologic malignancy. After 12 months of transdermal testosterone (Andropatch; 2.5-mg patches, 1 to 2 patches/d), significant improvements in physical vigor, low-density lipoprotein cholesterol levels, and activity score were found in the testosterone-treated group versus the placebo group. No significant changes in bone mineral density, mood, or sexual function were observed.

There is a concern that testosterone, as an anabolic agent, may be associated with the proliferation of cancer cells. There are no reports in the literature or evidence that this is true. We do not discuss prostate cancer in this article, in which testosterone may have a permissive effect and would be an absolute contraindication.

HIV

Although the prevalence of hypogonadism ranges from 30% to 50% in men who had HIV wasting before highly active antiretroviral therapy (HAART), it still occurs in about 20% to 25% of HIV-infected men treated with HAART [56,57]. Various mechanisms have been proposed for hypogonadism in HIV-infected men, although it is probably a result of a combination of these mechanisms. Primary hypogonadism in HIV-infected men could be caused by testicular atrophy due to opportunistic infections. Nonspecific interstitial inflammation and interstitial fibrosis were observed by De Paepe [58] in 32% of AIDS patients via autopsy examination. In this group of patients, the testes were infected with cytomegalovirus, *Mycobacterium avium-intracellulare*, and *Toxoplasma*. The autopsies also revealed atrophy due to chemotherapy in patients who had secondary neoplasms. Although therapeutic antifungals such as ketoconazole have been implicated in inhibition of steroidogenesis [59], data about effects of antiretroviral agents are limited and inconclusive [57].

Secondary hypogonadism is more common in HIV-positive patients. Malnutrition and acute and chronic illness in patients who have AIDS can cause significant weight loss and disrupt the HPG axis, causing hypogonadism [2]. Cytokines likely affect all levels of the HPG axis [60,61]. Interleukin-1 has been shown to inhibit gonadotrophin release and LH binding to Leydig

oxandrolone to reverse weight loss associated with COPD [75]. Direct testosterone replacement is more effective than the use of testosterone analogs because the functionality of patients does not seem to improve despite increases in lean body mass in studies with the testosterone analogs. In a randomized, placebo-controlled trial with men undergoing long-term glucocorticoid treatment, testosterone replacement improved lumbar spine bone mineral density and overall quality of life significantly, whereas nandrolone decanoate and placebo did not [76]. In addition, testosterone replacement has been shown to improve bone mineral density in men who have asthma who are taking oral glucocorticoids by 5% after 1 year of treatment, compared with no change in the placebo group [77,78]. Thus, testosterone replacement in hypogonadal men who have COPD or asthma may be recommended to reduce the risk of osteoporosis and to prevent loss of lean body mass.

Chronic liver disease

The prevalence of hypogonadism in chronic liver disease is unknown. In patients who have alcoholic liver disease, primary testicular failure can occur due to defective morphology of Leydig cells caused by ethanol [79] even before clinical signs of hypogonadism are present. The HPG axis is also affected, resulting in a diminished pulsatile secretion of LH [79]. The degree of hypothalamic hypogonadism correlates with the degree of liver damage in cirrhosis [80]. In men who have chronic hepatitis and who have lesser degree of liver damage, the HPG axis is not affected.

The diagnosis can be difficult because the serum level of SHBG is often higher than normal in patients who have chronic liver disease, leading to an overestimate of bioavailable testosterone. Therefore, free testosterone levels should be measured initially to assess the patient's endocrine status because hypogonadism is a significant risk factor for osteoporosis and is predictive of spinal fracture in patients who have chronic liver disease [81].

No studies have investigated bone mineral density with testosterone supplementation in men who have chronic liver disease. A retrospective study showed that testosterone gel improves muscle strength and increases survival in patients undergoing liver transplant who have chronic allograft failure [82]. To reduce the theoretical risk of inducing hepatocellular carcinoma, transdermal testosterone is preferred after discussing the risks and benefits of replacement with the patient. This would reduce exposure of the liver to high levels of testosterone associated with intramuscular injections and lead to more stable serum testosterone levels [81]. Even though testosterone replacement in patients who have chronic liver disease has not been studied thoroughly, it might provide some benefit in reducing the risk of osteoporosis and spinal fracture.

Chronic renal failure

About two thirds of men undergoing hemodialysis for end-stage renal disease have testosterone levels in the hypogonadal range [83,84]. Androgen

deficiency and decline in Leydig cell sensitivity to LH is associated with chronic renal failure even with a moderate reduction in glomerular filtration rate [85]. A serum factor present in uremia likely inhibits the LH receptor, thus rendering the Leydig cell less sensitive to LH stimulation [86]. The resultant reduction in testosterone production coupled with increased metabolic clearance of testosterone [87] causes low serum testosterone levels. Secondary hypogonadism also occurs in uremic men when the pulsatile LH secretion is diminished despite reduced negative feedback from low testosterone levels. The pulsatility is present, but the amount of LH released per pulse is reduced [85].

Renal transplantation reverses the combined form of hypogonadism observed in these patients. The use of nandrolone decanoate, a 19-nortestosterone derivative, resulted in a significant increase in lean body mass and physical functionality and in a decrease in fatigue in a randomized controlled trial with patients receiving long-term dialysis [88]. Singh and colleagues [84] reported that using two transdermal testosterone patches instead of one helped achieve mid-normal levels of testosterone in hypogonadal patients undergoing hemodialysis. The effects of testosterone replacement on lean body mass needs further study. Earlier studies demonstrated that although some men might benefit from testosterone replacement, in most men testosterone replacement alone fails to restore libido and erectile function despite restoration of normal serum testosterone levels [85]. A more recent pilot study with 12 patients who were given intramuscular testosterone injections and sildenafil reported a beneficial result [89]. More long-term studies are needed to determine the safety and efficacy of this combination treatment. Although further studies are needed to establish the benefit of testosterone therapy in hypogonadal men who have chronic renal failure, the use of testosterone derivatives might be beneficial in increasing lean body mass and functionality.

Rheumatoid arthritis

Men who have rheumatoid arthritis (RA) have low serum levels of free testosterone and LH [90] due to a hypothalamic/pituitary defect. One possible cause is long-term treatment of RA with nonsteroidal anti-inflammatory drugs, which are known to inhibit gonadotrophin release from the pituitary. Because androgens may be involved in tissue-specific immunosuppressive responses at the level of the synovial tissue in RA, low levels of testosterone may worsen disease activity [91]. Furthermore, androgen deficiency has been implicated in loss of BMD, resulting in osteoporosis in RA.

An open, uncontrolled study with oral testosterone undecanoate administration reported an overall 60% clinical improvement, a reduction of the number of affected joints, lower intake of nonsteroidal anti-inflammatory drugs, and improved libido at the end of 6 months without any relevant side effects [92]. A randomized, double-blind study using testosterone enanthate injections conducted by Hall and colleagues [93] failed to show any

significant beneficial effect of testosterone replacement on disease activity and bone density, possibly because the subjects were undergoing steroid treatment for RA, a significant contributor to decreased bone density. Further studies are needed to determine if higher doses of testosterone would be beneficial when patients are undergoing treatment with steroids.

Summary

In relatively healthy men who have hypogonadism, testosterone replacement therapy has been shown to improve sexual function, mood, lean body mass, and bone density. Low serum testosterone in acute and chronic disease is fairly common and is multifactorial due to the combination of weight loss, stress, specific medications, and infections. Few studies have been done evaluating the effects of replacement in such men who have systemic diseases. Little information is available regarding testosterone treatment in the face of acute illness (although benefit in burn patients is likely); therefore, testosterone treatment cannot be routinely recommended. Most data suggest that testosterone can be offered to patients who have chronic disease unless there is a specific contraindication (eg, prostate cancer, breast cancer, or untreated sleep apnea). Testosterone therapy is generally well tolerated [94]. Elevations of hematocrit and prostate-specific antigen levels should be monitored. Although the treatment of hypogonadism in systemic disease is controversial and needs further study, testosterone can be offered to patients who have systemic diseases for symptomatic relief. Although it is unlikely that testosterone will affect the underlying disease, further study is needed to understand the effects of quality of life and maintenance of lean body mass on long-term health outcomes.

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