Testicular Dysfunction in Human Immunodeficiency Virus–Infected Men

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This review pertains to gonadal function in men with human immunodeficiency virus (HIV) infection, who often exhibit clinical and biochemical evidence of hypogonadism. Hypogonadotropic hypogonadism appears to be the most commonly encountered abnormality, although complete anterior pituitary insufficiency and primary gonadal failure have been reported. Levels of sex hormone–binding globulin (SHBG) are either unchanged or increased. Plasma levels of estrogens, progesterone, androstenedione, dehydroepiandrosterone sulfate (DHEA-S), and prolactin vary. Pathologically, except for involvement by opportunistic infections, no significant abnormality in the hypothalamic-pituitary area has been described, but evidence of orchitis is commonly present. The cause(s) of these abnormalities remains unclear. The possible factors leading to hypogonadism in HIV-infected men include HIV infection itself, opportunistic infections, chronic debilitating illness, and effects of cytokines on the hypothalamic-pituitary-gonadal axis. Further studies are needed to clarify the cause(s) of testicular dysfunction in HIV-infected men and its clinical significance, treatment, relevance to the progression of HIV infection, and influence on the immune system.

ALTHOUGH STUDIES of gonadal function in women with acquired immune deficiency syndrome (AIDS) are needed, to our knowledge none have been published so far.[1] Therefore, this review will focus on gonadal function in men with human immunodeficiency virus (HIV) infection. The knowledge in this area is still largely in the descriptive stage, and our understanding of the pathogenesis of gonadal abnormalities in HIV-infected individuals is hindered by complicated interactions of HIV infection, opportunistic infections, malignancies, chronic illness, cachexia, illicit drug use, and therapeutic interventions.[1-5] Further adding to the difficulties in reviewing this field is the fact that many of the cited studies preceded the current 1993 Centers for Disease Control classification of AIDS.[6] The investigators in these studies therefore commonly used the now-invalid term AIDS-related complex (ARC). Some of the HIV-positive patients without opportunistic infections who were assigned to the asymptomatic HIV-seropositive group in previous studies would be classified as AIDS in the current Centers for Disease Control classification if their CD4 cell count was less than 200/μL. Because of the lack of CD4 cell counts in earlier studies, it is impossible to determine the appropriate stage of HIV infection according to the current Centers for Disease Control classification for patients with ARC or in HIV-positive asymptomatic groups. We therefore continue to use these terms in the same way as in the original studies.

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PATHOLOGIC STUDIES

Postmortem studies of pituitary glands and testes of HIV-infected individuals are limited to patients who died of AIDS and its complications.

HIV infection in the central nervous system is well documented[7]; however, to our knowledge, there are no studies localizing HIV to the hypothalamic/pituitary area. A postmortem study of pituitary glands from 49 patients with AIDS reported by Sano et al[8] found a 12% (six of 49) infection rate in the adenohypophysis: five patients had cytomegalovirus (CMV) and one had *Pneumocystis carinii* involvement. In addition, two patients had CMV and one had *Toxoplasma gondii* infection of the neurohypophysis. In all of the patients, these pathologic processes were associated with generalized and/or cerebral infection by the same organisms. The prevalence of noninfectious lesions, such as hyperplastic nodules and microadenomas, in HIV-infected patients was similar to that in age-matched controls. Neither Kaposi's sarcoma nor lymphoma was noted in the pituitary glands.

In contrast to the rare pathologic involvement of the pituitary in AIDS, involvement of the testes appears to be more common. Histologically, testes of patients with AIDS often exhibit azoospermia, interstitial tissue fibrosis, thickening of the seminiferous tubule basement membrane, and tubular hyalinization.[9-11] In addition, variable degrees of spermatogenic arrest, numerous foci of germ cell degeneration, decreased number of Leydig cells, blockage of the epididymis, and lymphocytic infiltration of the interstitial tissue are often present.[9,10,12] Pudney and Anderson[9] observed the following in testes of 43 AIDS patients: 68% complete azoospermia, 28% maturation arrest, and only 4% normal spermatogenesis. These findings, together with the histologic picture mentioned earlier, are consistent with orchitis and the progressive loss of testicular function in AIDS.[9-12] It is not yet known whether the orchitis found in AIDS patients is a nonspecific sequela of viremia, a direct effect of HIV on reproductive tissues, or a result of other factors such as immunodeficiency.

Identification of HIV-related P17 protein by staining with monoclonal antibodies in the testes of men with AIDS has raised the possibility of a direct effect of HIV on the

testes.[12,13] In the study reported by Pudney and Anderson,[9] white blood cells infiltrating the testes (T-lymphocytes and macrophages) were shown to have CD4 receptors, indicating their capability of hosting HIV. Macrophages and cells of lymphocytic morphology were observed migrating across the boundary walls of hyalinized seminiferous tubules to enter the lumen through the compromised or destroyed blood-testis barrier; these cells were thus appearing in semen.[9] Immunochemical studies of the urogenital system in AIDS showed HIV protein expression in lymphocytic/monocytic cells of the seminiferous tubules and interstitium of the testes in nine of 23 cases tested.[9] In this study, there was no evidence of active HIV infection in germ cells or Sertoli cells of the seminiferous tubules or other epithelial cells lining the efferent ducts.[9] However, Nuovo et al[14] demonstrated HIV DNA in the testes in 11 of 12 men with AIDS. They used polymerase chain reaction in situ hybridization, which is more sensitive than either in situ hybridization or the immunocytochemical techniques used by Pudney and Anderson.[9,14,15] HIV DNA was found in 5% to 20% of the spermatogonia and spermatocytes, 1% of the spermatids, and rare macrophages, but not in Sertoli cells, Leydig cells, or endothelial cells of the testes studied with this technique.[14] Direct HIV infection of the spermatogonia and their progeny may explain the histologic changes observed in the testes of AIDS patients and the mechanism of sexual transmission of HIV.

A study by De Paepe et al[16] focused on opportunistic infections of the testes in men with AIDS. They found that CMV, *Mycobacterium avium-intracellularis,* or *Toxoplasma gondii* involved the testes in 39% (22 of 56) of AIDS patients who had systemic evidence of these opportunistic infections. Chabon et al[11] focused on tuberculous involvement of the testes and found a 25% (seven of 28) incidence of this infection in the testes of patients with AIDS and systemic tuberculosis.

In summary, it appears that both the hypothalamic-pituitary area and the testes of AIDS patients may exhibit pathologic changes that may be due to HIV infection itself, opportunistic infections, or nonspecific effects of illness. Pathologic changes in the testes appear to be much more common than in the hypothalamic-pituitary area.

HYPOGONADISM

Patients with AIDS may complain of decreased libido, muscle wasting, loss of body hair, gynecomastia, and impotence.[17,18] Although severe clinically significant hypogonadism is rare, laboratory evidence of primary or secondary hypogonadism is common in AIDS.

To our knowledge, there has been only one report of a patient with AIDS (and central nervous system toxoplasmosis) who developed complete anterior pituitary insufficiency, which was manifested by secondary adrenal insufficiency, hypothyroidism, and hypogonadism.[19] Additional endocrine evidence of anterior pituitary failure in this patient included lack of growth hormone response to hypoglycemia and absent thyrotropin and prolactin responses to thyrotropin-releasing hormone. Neurohypophyseal function was normal, as indicated by adequate urine concentration after an overnight fast. At the postmortem examination, the posterior lobe of the pituitary was normal. It is of interest that in this case the inflammatory infiltrate caused by the Toxoplasma did not affect the pituitary or hypothalamus directly; Toxoplasma parasites were present in cerebral abscesses, but not in the large necrotic pituitary. Thus, the relation of pituitary insufficiency to HIV or Toxoplasma infection in this patient remains unclear. Sullivan et al[20] reported partial anterior hypopituitarism (hypothyroidism and hypogonadism) in a patient with hypothalamic CMV infection and AIDS. Hypothalamic-pituitary-adrenal axis and growth hormone secretion were not evaluated, although a morning cortisol level was found to be in the normal range. This patient's hypogonadism improved with ganciclovir, high-dose glucocorticoid, and L-thyroxine therapy, thus demonstrating that in some cases hypogonadism may be reversible with treatment of the underlying infectious process.

Although complete pituitary insufficiency in AIDS is rare, diminished gonadotropin secretion appears to occur more commonly. Abnormalities of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) have been described in patients with AIDS and are discussed later.

When evaluating the literature, one should keep in mind several factors that can affect the investigator's conclusions. In some studies, measurements of gonadotropin (as well as prolactin) levels could be affected by the preheating of plasma to 56°C, the procedure used in some facilities for inactivation of HIV. In the study reported by Hancock et al,[21] the mean reduction in circulating hormone levels after preheating the plasma was 5% for FSH, 16% for LH, and almost 30% for prolactin. Of interest is the fact that testosterone measurements were not significantly affected by preheating. When evaluating hypothalamic-pituitary-gonadal function in HIV-infected individuals who are users of narcotic drugs, one also has to keep in mind that these substances can alter gonadal function. Plasma testosterone levels are often subnormal in heroin users, as well as in patients treated with methadone, which can also impair sperm motility.[22] Therapeutic agents may also contribute to the development of testicular damage and hypogonadism in AIDS: the antifungal agent ketoconazole[23] and ganciclovir, used for treatment of CMV retinitis,[22] are potent inhibitors of steroidogenesis and may produce oligospermia, azoospermia, gynecomastia, and reduced testosterone levels.

Dobs et al[17] reported that 38% (24 of 63) of HIV-infected males at different stages of infection had decreased serum testosterone levels. The prevalence of this abnormality varied with the stage of infection: it affected 6% (one of 16) of HIV-seropositive asymptomatic individuals, 44% (three of 7) of ARC patients, and 50% (20 of 40) of AIDS patients. Hypogonadotropic hypogonadism accounted for 75% (18 of 24) of hypogonadal patients. Seven patients with hypogonadotropic hypogonadism in whom a gonadotropin-releasing hormone (GnRH) test was performed had a normal response of gonadotropins to GnRH, suggesting a functional disorder of the hypothalamus, ie, failure to release GnRH normally. (Although the lack of response to GnRH bolus does not differentiate between hypothalamic and

pituitary causes of hypogonadism, normal response does exclude significant pituitary gonadotropin deficiency.) This study included a heterogenous patient population: 76% were homosexual or bisexual, 6% were intravenous drug users, 6% had transfusion-related disease, and 13% had no apparent risk factors.

In contrast to the study reported by Dobs et al,[17] Croxson et al[18] reported findings consistent with primary hypogonadism in men with AIDS. They compared total testosterone and gonadotropin levels in asymptomatic HIV-positive patients, ARC patients, and AIDS patients; HIV-negative homosexual men served as controls. As a group, AIDS patients had significantly decreased total testosterone levels and increased serum LH and FSH levels; sex hormone–binding globulin (SHBG) levels were normal, so that free-testosterone levels were decreased in proportion to total testosterone. Differences in serum testosterone concentrations between HIV-seropositive asymptomatic patients, ARC patients, and controls were not statistically significant. LH levels were higher than control levels in patients with ARC or AIDS, whereas FSH levels were elevated only in men with AIDS.

Lefrere et al[24] reported that hypogonadal patients with AIDS had either normal or increased levels of gonadotropins. Of interest was the fact that there were no correlations between the decrease in androgens and the increase in either LH or FSH.

Raffi et al[25] observed a similar lack of correlation between testosterone and gonadotropin levels. They found decreased total testosterone levels in 29% (eight of 29) patients with AIDS, whereas LH levels were normal (inappropriately low?) and FSH levels were elevated. Inhibin level was not measured. The pituitary response to GnRH was normal in all the subjects. This study also found significant correlations between testosterone levels and CD4 cell counts.

While examining the chronobiology of testosterone levels in AIDS, Villette et al[26] found that 24-hour mean plasma testosterone levels were reduced by only 9% as compared with those of normal subjects. The lowest individual plasma testosterone levels among AIDS patients were found at 8:30 AM and 12:30 PM. In the same study, plasma testosterone rhythms among asymptomatic HIV-seropositive patients were not significantly different from those of normal subjects. There were no patients with ARC in the study.

In contrast to studies that demonstrated hypogonadism in AIDS, Merenich et al,[27] who examined the gonadal axis in asymptomatic HIV-seropositive individuals, found that total and particularly free-testosterone levels were increased in these patients as compared with normal controls. Basal LH also tended to be higher and LH response to GnRH was significantly increased in the HIV-infected group. The hyperdynamic response of LH to GnRH in the face of elevated testosterone was thought to result from some abnormality at the hypothalamic-pituitary level.

Thus, with the exception of the study reported by Merenich et al,[27] the most common gonadal abnormality found in HIV-infected men is decreased testosterone with normal (inappropriately low) or only slightly increased gonadotropin levels, normal gonadotropin response to GnRH, and absence of radiologic or postmortem evidence of structural hypothalamic or pituitary abnormalities. These findings suggest a functional disorder of hypothalamic GnRH secretion.[17] Since HIV is present in the central nervous system in infected patients,[7] it is possible that some cases of hypogonadotropic hypogonadism may result from viral damage to the hypothalamus or pituitary. However, this theoretic possibility has not yet been proven.

Disturbance of the hypothalamic-pituitary-gonadal axis may also be a nonspecific consequence of the underlying illness rather than of HIV infection itself.[17,25] It is well known that patients with a variety of systemic illnesses and wasting syndromes may develop hypogonadotropic hypogonadism.[28] It is possible that this hypogonadism is due to a release of cytokines by the activated phagocytic cells of the immune system, since cytokines may suppress reproductive function at several levels.[29]

It has been shown, for example, that in healthy individuals infusion of tumor necrosis factor (the levels of which are elevated in some patients with HIV infection[30]) affects the hypothalamic-pituitary-testicular axis at multiple levels, causing a decrease in circulating testosterone concentration.[31] Interleukin-1 directly injected into the third ventricle of animals inhibits pulsatile secretion of GnRH.[32] Interleukin-1a, produced locally within the testes, has been shown to inhibit Leydig cell secretion of testosterone and may have a paracrine role in modulating gonadal function. Overexpression of interleukin-2 in transgenic mice results in testicular atrophy and spermatogenic arrest.[32] A variety of other locally produced cytokines may also alter testicular function.[33]

To summarize these studies (Table 1), it appears that gonadal function in patients with HIV infection varies significantly and may depend on the stage of illness. In asymptomatic HIV-positive men, the pituitary-gonadal axis may be either normal or even somewhat hyperactive, resulting in elevated LH and testosterone levels. However, as the disease progresses, the incidence of hypogonadism increases and ranges between 29% and 50% in patients with full-blown AIDS.[17,25] Both primary and secondary hypogonadism have been observed.[17,18,24,25] Most cases of hypogonadism in HIV-infected men are probably caused by a combination of factors. These include chronic illness and wasting, producing nonspecific hypothalamic-pituitary dysfunction also seen in other chronic systemic illnesses, or infection of the hypothalamic-pituitary area and the testes by HIV or opportunistic agents.

SHBG

There is relatively little information regarding SHBG levels during HIV infection. Merenich et al[27] observed normal SHBG levels in HIV-seropositive asymptomatic patients. Dobs et al[17] and Croxson et al[18] found normal levels of SHBG in patients with AIDS. Lambert et al[34] found normal SHBG levels in patients with asymptomatic HIV-seropositivity, ARC, and AIDS; there were no differences in SHBG levels between groups. However, in a detailed study reported by Martin et al,[35] SHBG levels in

Table 1. Summary of Changes in Gonadal and Pituitary Hormone Levels in Men With Asymptomatic HIV-Seropositivity, ARC, and AIDS

Study	No. of Patients	Stage of HIV Infection (no.)			Risk Factors	Use of Medications Known to Affect Reproductive Hormones	Biochemically HypogonadalMen (%)			Changes in Steroid Hormones			Pituitary Hormones		
		Asymp HIV+	ARC	AIDS			Asymp HIV+	ARC	AIDS	Asymp HIV+	ARC	AIDS	Asymp HIV+	ARC	AIDS
Dobs et al,[17] 1988*	70	19	9	42	76% Homosexual 6% IVDA 6% Transfusion 13% No apparent risk factor	NA	6	44	50	T↔	T↓	T↓	LH NA FSH NA PRL↔	LH NA FSH NA PRL↔	LH↓ FSH↓ PRL↔
Croxson et al,[18] 1989†	85 (including 26 HIV⁻ controls)	32	7	20	100% Homosexual	None	NA	NA	NA	T↔ E_2↔	T↔ E_2↔	T↓ E_2↔	LH↔ FSH↔ PRL↔	LH↔ FSH↔ PRL↑	LH↑ FSH↑ PRL↑
Raffi et al,[25] 1991‡	67	12	27	28	NA	None	NA	NA	29	T↑	T↓	T↓	LH↔ FSH↓	LH↔ FSH↔	LH↔ FSH↑
Merenich et al, [27] 1990†	67 (including 27 HIV⁻ controls)	40	0	0	60% Homosexual 7% IVDA 28% Heterosexual contact 5% No apparent risk factor	None	NA	NA	NA	T↑ E_2↔	NA	NA	LH↔ FSH↔ PRL↔	NA	NA
Lefrere et al,[24] 1988*	16	5	0	11	100% Homosexual	None	NA	NA	NA	NA	NA	T↓	NA	NA	LH↔ FSH↔
Gorman et al,[42] 1992†	200 (including 79 HIV⁻ controls)	47	74	NA	NA	2% of HIV+ 1% of controls on anti-psychotics	NA	NA	NA	NA	NA	NA	PRL↔	PRL↔	NA
Christeff et al,[44] 1992†	103 (including 35 HIV⁻ controls)	15	21	32	100% Homosexual	None	NA	NA	NA	T↑ DHEA↑ DHEA-S↔ A↑ E_2↔ E_1↑ P↔ 17OHP↑	T↔ DHEA↓ DHEA-S↔ A↔ E_2↔ E_1↑ P↓ 17OHP↑	T↔ DHEA↓ DHEA-S↔ A↔ E_2↑ E_1↑ P↓ 17OHP↑	NA	NA	NA

Abbreviations: NA, not available; T, testosterone; E_2, estradiol; A, androstenedione; E_1, estrone; P, progesterone; 17OHP, 17 α-hydroxyprogesterone; PRL, prolactin; Asymp HIV+, asymptomatic HIV-seropositive; HIV⁻, HIV seronegative; IVDA, intravenous drug abuse; ↔, no change; ↑, increase; ↓, decrease.

*Results were reported compared with normal values of the assay used.

†Results were reported compared with HIV⁻ men.

‡Results were reported compared with asymptomatic HIV+ men.

patients with a range of HIV infection (total of 64 patients that included asymptomatic HIV-positive individuals and patients with ARC and AIDS) were found to be 39% to 51% above control levels (67 control subjects were examined).[35] The increase seemed to become more pronounced as the disease progressed. In addition, binding affinity of SHBG for testosterone was higher in patients with AIDS. This combination resulted in lower free-testosterone levels.

The cause of elevated serum levels of SHBG observed in some AIDS patients is unclear. However, it is tempting to speculate that altered insulin dynamics are involved. Insulin has been shown to suppress SHBG production by the liver both in vitro and in vivo.[36-38] In hyperinsulinemic insulin-resistant patients, SHBG is commonly suppressed.[38,39] However, patients with HIV infection appear to exhibit increased sensitivity to insulin and thus may have lower-than-normal circulating insulin levels.[40,41] This may lead to an increase in SHBG. Further studies are needed to evaluate SHBG production and mechanisms of its alteration in AIDS.

PROLACTIN

Serum prolactin levels in patients with HIV infection were examined by several groups of investigators. A problem with such studies is that prolactin is a stress hormone that increases nonspecifically in patients with physical or psychologic stress.[28]

Croxson et al[18] examined prolactin levels in HIV-negative homosexual men, asymptomatic HIV-positive homosexual men, and ARC or AIDS patients. Men who were abusing drugs or taking major psychoactive medications were excluded from this study, thus eliminating some of the major causes of hyperprolactinemia that may not be specific to HIV infection. The investigators found that 59% (19 of 32) of asymptomatic HIV-positive men, 71% (five of seven) of men with ARC, and 80% (16 of 20) of men with AIDS had prolactin levels in excess of the mean for the control group. Mean prolactin levels of patients with ARC and AIDS were significantly higher than in HIV-negative men, but only approximately 20% of these subjects had absolute, although modest, degrees of hyperprolactinemia.

Dobs et al[17] did not find any difference in prolactin levels between HIV-positive men (asymptomatic, ARC, or AIDS) and normal controls. Six percent of their patients were intravenous drug abusers. Other studies, which mostly excluded narcotic and phenothiazine users, found no increase in prolactin levels in HIV-positive individuals, including those with AIDS.[27,42,43] Thus, it appears that elevation of prolactin is not a consistent finding in patients with AIDS, and it is not clear whether a mild elevation of prolactin, observed in some patients, contributes to hypogonadism. In those patients whose prolactin is elevated, the abnormality could be explained by a nonspecific effect of illness, by effects of HIV on dopamine metabolism in the central nervous system, by drugs (such as opiates, phenothiazines, or cocaine), or by the actions of cytokines released by HIV-infected macrophages.[18,22]

ESTROGENS, PROGESTERONE, ANDROSTENEDIONE, AND DEHYDROEPIANDROSTERONE

Information regarding estrogen and progestin levels in men with HIV infection is limited to a few studies. Croxson et al[18] found similar estradiol levels in HIV-negative homosexual men and HIV-positive homosexual men who were either asymptomatic or suffered from ARC or AIDS. Merenich et al[27] observed no difference in estradiol levels between HIV-positive asymptomatic homosexual men and seronegative heterosexual healthy controls.

In a study of 68 HIV-infected homosexual men, Christeff et al[44] found essentially normal estradiol levels in men with asymptomatic infection or ARC, but higher levels in patients with AIDS. A statistically significant 30% to 50% increase in estrone levels was found in all three stages of HIV infection in the same study, whereas progesterone levels were found to be decreased in some patients with AIDS. Androstenedione concentrations were 60% above control levels in the early stages of HIV infection, but declined into the normal range as the disease progressed. Serum dehydroepiandrosterone (DHEA) concentrations were elevated in patients with asymptomatic HIV infection, but were decreased in ARC and AIDS. Serum DHEA-sulfate (DHEA-S) values in all groups of HIV-positive patients were not statistically different from control levels.[44] The investigators suggested that the high estrone concentration may result from enhanced conversion of precursor adrenal androgens in AIDS patients. The low progesterone concentrations in some patients were explained by the possibility that adrenal steroidogenesis in these patients may be shifted toward preferential production of glucocorticoids.[44]

It is difficult to interpret the significance of these studies, not only because of their variable results, but also because serum levels of estrogens, progesterone, androstenedione, DHEA, and DHEA-S in men are not direct indicators of gonadal function, since they can be of adrenal or gonadal origin and can also be formed by peripheral conversion of adrenal or gonadal precursors.

IMMUNE FUNCTION AND SEX HORMONES

Although the relationship between glucocorticoids and the immune system is well established, the effects of sex steroids on the immune system are much less clear. There is evidence that, overall, estrogens may enhance the immune response and androgens and progestins may be inhibitory.[45,46] Estrogens may have a direct effect on B lymphocytes, stimulating their differentiation and immunoglobulin synthesis; they inhibit suppressor T lymphocyte activity and facilitate helper T lymphocyte maturation, and they also influence macrophage maturation and function.[46] It has been demonstrated that androgens cause diminished antibody response by suppressing maturation of B cells. They further affect immune response by increasing activity of suppressor T lymphocytes.[46,47]

If the results of these in vitro and animal studies are applicable to humans, changes in gonadal hormone levels (some increase in estrogens and decrease in androgens,

resulting in a decreased testosterone to estrogen ratio) in patients with AIDS could be viewed teleologically as an attempt to improve the immune response in the face of an assault on the immune system by HIV. However, the relatively mild degree of sex hormone changes observed in AIDS makes it unlikely that the sex hormone changes alter immune function to any significant extent.

CLINICAL SIGNIFICANCE

The clinical significance of changes in sex hormone levels in AIDS patients is unclear, unless the patient presents with impotence and/or loss of libido that cannot be explained simply by the severity of his HIV-related illness and/or drug use.

Androgen treatment of hypogonadal men, in addition to restoring normal erectile function, has several other beneficial effects. These include reduction in urinary excretion of nitrogen, sodium, potassium, phosphate, sulfate, and chloride, induction of weight gain, prevention of bone loss, increase in muscle mass, and a sense of well-being.[48,49] These effects of androgens make them potentially attractive in the treatment of wasting syndrome.

HIV wasting syndrome is a common complication of AIDS; the possible etiologies include anorexia, malabsorption, gastrointestinal malfunction, neoplasms, infectious diseases, diarrhea, drug abuse, hypermetabolism, and hypogonadism.[50,51] Coodley et al[51] found that AIDS patients with wasting (n = 14) had lower total- and free-testosterone levels as compared with AIDS patients without wasting (n = 18). In both groups of patients, CD4-positive lymphocyte counts were less than 200/μL. There was no statistically significant difference in mean CD4 cell counts, although there was a tendency for a lower CD4 cell count in patients with wasting. Decreased androgen levels correlated with the degree of weight loss, but the investigators concluded that it was unclear whether hypogonadism was a cause or result of wasting.

Although it is tempting to prescribe androgens for HIV-infected men with wasting syndrome because of the anabolic action of androgens, it is unclear whether androgen treatment will benefit nonhypogonadal HIV-infected men. Ordinarily, testosterone treatment does not increase the weight of undernourished or debilitated individuals. It fails to promote anabolism in acute illness, trauma, or chronic illnesses.[48] However, in a nonblinded study, Jeantils et al[52] reported that four eugonadal men with AIDS who received oral testosterone preparation for 2 months had an increase of 14.8% in weight and 13.5% in body mass index as compared with baseline values obtained before the study.

Since the effects of androgen replacement therapy in HIV-infected individuals without clinical evidence of hypogonadism have not been studied systematically, and since the gonadal hormone changes could be due to the nonspecific effects of illness, as discussed earlier, we would not recommend either routine screening of patients with HIV infection for gonadal abnormalities or any specific hormonal therapy if such abnormalities are found incidentally. This recommendation may change and routine screening of all HIV-infected men for hypogonadism may become advisable if clinical trials demonstrate clear benefits of supplemental testosterone therapy in patients without clinical manifestations of hypogonadism. At present, we recommend supplemental testosterone therapy if the patient presents with clinical evidence of hypogonadism and if hypogonadism is confirmed by hormonal studies. When prescribing testosterone to HIV-infected men, the potential beneficial effects should be weighed against the known side effects of androgen treatment, including the potential negative impact of androgens on immune function. Careful clinical trials in well-characterized hypogonadal and eugonadal HIV-infected men are needed to evaluate the beneficial effects of androgen treatment, not only on reproductive function but also on the wasting syndrome.

CONCLUSION

A variety of abnormalities of gonadal function have been described in patients with HIV infection. To clarify the cause(s) of these abnormalities and their biologic significance, relevance to progression of HIV infection, and interplay with the immune system and to determine appropriate indications for androgen therapy in HIV-infected men will require further study.

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