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Androgen therapy in AIDS wasting

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Hypogonadism in HIV-infected men has been well described, having a prevalence of about 30%. Its aetiology is a combination of non-specific changes from chronic and acute illness, and specific effects due to HIV infection. A depressed serum testosterone level has been associated with viral or infectious invasion of the endocrine organs, and with medications commonly used in treating HIV infection. Recently, many have noted the association between decreased serum testosterone in men and women, and the wasting syndrome of HIV infection, particularly with a reduction in lean body mass. Our understanding of the risks and benefits of testosterone therapy in non-HIV infected men has grown significantly. Treatment in this population can improve sexual function, quality of life parameters and body composition. Based on this information, a few studies have been carried out, and more are being planned to test the hypothesis that therapy with testosterone or its analogues can benefit HIV-infected men and women with wasting and/or low circulating androgen concentrations. To date, the studies have been inconclusive. Not all studies have shown a statistical benefit of androgen therapy on weight, muscle mass or quality of life. Testosterone is now available in several forms for dosing, which has improved compliance and ease of administration. Its potential risks to the prostate or serum lipids should be monitored closely. Although the beneficial effects of androgenic steroids in HIV-infected men have not been demonstrated clearly, short-term studies suggest that testosterone supplementation may improve metabolic outcomes in HIV-infected men with androgen deficiency.

Key words: androgens; wasting; testosterone; lean body mass; anabolic steroids.

HYPOGONADISM IN HIV DISEASE

Epidemiology of hypogonadism

A number of endocrine abnormalities, including adrenal insufficiency, hypercortisolism, diabetes mellitus and hypopituitarism, have been reported in HIV-infected men (Sellmeyer and Grunfeld, 1996). Hypogonadism occurs in approximately 30% of HIV-infected men (Dobs et al, 1988). The percentage of men with hypogonadism may be underestimated

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if only serum total testosterone is measured. The major binding protein for testosterone, sex hormone-binding globulin (SHBG), is increased in HIV infection relative to a control population (Martin et al, 1992). Therefore, free or bio-available testosterone (both the free hormone and that which is loosely bound to circulating albumin) should be measured when the total testosterone is at the lower end of normal.

Adrenal androgen levels have been reported to be low in HIV infection (Honour et al, 1995), with a possible association with moderate immunosuppression. Findling et al (1994) postulated that there may be a shift away from dehydroepiandrostenedione (DHEA) to cortisol in patients with HIV. Since DHEA is a weak androgen, the clinical significance of the decline in DHEA is not clear (Rabkin and Ferrando, 1997).

Although menstrual irregularities and infertility are common in other disease states, these characteristics have not been well documented in HIV-infected women (Ellerbrock et al, 1996). However, HIV-infected women with wasting have lower serum testosterone levels than HIV-negative women (Grinspoon et al, 1997).

Pathophysiology of hypogonadism in HIV infection

The mechanisms of hypogonadism in HIV-infected men are complex and include the general effects of chronic and acute illness, malnutrition, cytokines and the specific effects of HIV infection (Sellmeyer and Grunfeld, 1996). As the HIV epidemic continues, age-related declines in serum testosterone level, seen in the general population, can now be seen in an ageing AIDS cohort. The age-related decrease in testosterone concentration is attributed to defects at the hypothalamic, pituitary and testicular levels. Based on the Massachusetts Longitudinal Study on Aging, approximately 15% of men aged 65 years and above have a serum level below the normal range.

Chronic illness and weight loss are commonly associated with hypogonadism. For example, women with anorexia nervosa are often amenorrhic, and hospitalized men, particularly those with weight loss, have a low serum testosterone level (Garfinkel et al, 1975; Smith et al, 1975; deKrester, 1979; Morley and Melmed, 1979; Pont et al, 1984; Hoffer et al, 1986). The mechanism of illness-related hypogonadism is mediated primarily at the hypothalamus–pituitary level. In post-menopausal women admitted to an intensive care unit, the serum follicle stimulating hormone level was lower than that in age-matched, healthy controls (Warren et al, 1977).

The hypogonadism observed during the course of HIV infection may also be specifically related to the infection or its complications. Hypopituitarism due to pituitary infiltration with granulomatous invasion or toxoplasmosis has been reported (Ferreiro and Vinters, 1988). The HIV can directly invade the Leydig cells, resulting in primary testicular dysfunction (Reichert et al, 1983; Chabon et al, 1987; McCutchan et al, 1993a,b)

Medications used in the treatment of HIV can lower sex steroid concentrations. Megestrol, used as an appetite stimulant, is a progestational agent that inhibits gonadotropins (Engelson et al, 1996). Ketoconazole and

fluconazole (Pont et al, 1982, 1984) inhibit several enzymes in the steroidogenic pathway. Treatment with the anti-viral agent gancyclovir (Chaachoua et al, 1987) has also been associated with depressed serum testosterone levels. Alkylating chemotherapeutic agents commonly cause primary testicular damage.

Consequences of hypogonadism in HIV infection

The clinical consequences of hypogonadism can be subtle in post-pubertal men. Sexual dysfunction and a decreased sense of well-being have been reported in 100% and 65% respectively of men attending an HIV clinic in New York (Rabkin et al, 1995). The high prevalence of sexual dysfunction in HIV-infected men (Tindall et al, 1994) probably diminishes their quality of life (Chalmers et al, 1992; Cohen et al, 1993).

Other potential problems reported in healthy, hypogonadal men who are not HIV-infected include depression, decreased sexual hair, reduced muscle mass and decreased bone density (Bhasin and Bremner, 1997). With the increasing life expectancy of HIV-infected men, the long-term effects of androgen deficiency may become clinically significant. For example, androgen deficiency may lead to osteoporosis (Katznelson et al, 1996).

Relationship of hypogonadism to HIV-associated wasting

Wasting is presently defined as a loss of more than 10% of base-line weight (Weinroth et al, 1995). It is not based on the change relative to ideal body weight or percentage lean body mass. The magnitude of lean body mass depletion is a strong predictor of mortality in HIV-infected men—a better one than CD4 T-cell counts (Kotler et al, 1989; Suttman et al, 1995). Weight loss results from an imbalance between nutritional intake, especially during opportunistic infections, and resting energy expenditure (Schambelan et al, 1996). The role of cytokines in the pathophysiology of HIV-associated wasting or hypogonadism is unclear (Weinroth et al, 1995; Hellerstein et al, 1996).

Weight loss in HIV-infected men correlates with a reduction in circulating testosterone level (Coodley et al, 1994). In a prospective analysis of the Multicenter AIDS Center data, we found that free, bio-available and total testosterone levels gradually decreased in those with AIDS and that reductions in bio-available testosterone can be observed with small degrees of weight loss before true wasting occurs (Dobs et al, 1996). Androgen levels correlate with changes in lean body mass, muscle mass and exercise capacity in hypogonadal men with AIDS-associated wasting (Grinspoon et al, 1996). Hypogonadism also correlates with lymphocyte depletion and CD4 lymphocyte cell counts (Laudat et al, 1995; Christeff et al, 1996).

Although the prevalence of menstrual irregularities is not markedly increased in HIV-infected women (Ellerbrock et al, 1996), serum testosterone levels are lower in HIV-infected women compared with healthy women and correlate with a decreased body cell mass (Grinspoon et al, 1997; Engelson et al, 1996).

SAFETY AND EFFICACY OF TESTOSTERONE THERAPY

Testosterone therapy has numerous advantages in the non-HIV-infected man. Studies using androgens in HIV-infected individuals are few and are outlined in Table 1.

Table 1. Effects of exogenous androgens in HIV infected men and women.

Author	Treatment	Outcome measures	Result
Wagner and Rabkin (1998)	i.m. testosterone	Sexual function	89% increase
$N=19$, uncontrolled study,	400 mg bi-weekly	Quality of life	71% increase
3 months		Weight	2.3 kg increase
Coodley and Coodley (1997)	Testosterone i.m.	Quality of life	$P=0.03$
$N=40$, placebo controlled,	200 mg bi-weekly	Weight gain	NS
3 months		Muscle strength	$P=0.08$
Gold et al (1996)	Nandrolone deconoate	Quality of life	$P<0.05$
$N=17$, uncontrolled,	i.m. bi-weekly	Lean body mass	$P<0.05$
16 weeks			
Bucher et al (1996)	Nandrolone 100 mg	Weight gain	$P<0.05$
$N=73$, placebo controlled,	i.m. weekly	Haematocrit	$P<0.05$
12 weeks			
Poles et al (1995)	Oxandrolone 10 mg	Weight gain	+5.85 kg
$N=21$, uncontrolled,	b.i.d. orally	Body cell mass	+3.13 kg
60 days			
Berger et al (1996)	Oxandrolone 15 mg	Weight gain	+2.04 kg difference
Placebo controlled,	daily orally		from placebo
12 weeks			
Hengge et al (1996)	Oxymetholone	Quality of life	$P<0.05$
$N=14$, open label, matched		Weight gain	+8.2 kg increase
controlled, 30 weeks			
Dobs et al (1998)	Testosterone patch on	Sexual function	NS
$N=130$, placebo controlled,	scrotum, 5 mg daily	Quality of life	$P=0.07$
3 months		Weight gain	NS
Bhasin et al (1998)	Non-scrotal testosterone	Weight gain	NS
$N=41$, placebo controlled,	patch, 5 mg daily	Lean body mass	+1.35 kg ($P=0.0254$)
3 months		Emotional stability	$P=0.01$
Grinspoon et al (1998)	Testosterone enanthate	Weight	NS
Placebo controlled,	300 mg every 3 weeks	Lean body mass	+1.9 kg ($P=0.041$)
3 months		Quality of life	$P=0.04$

i.m. = intramuscular; t.i.d. = three times daily; NS = not significant; b.i.d. = twice daily.

Effects on sexual and psychological function

Using questionnaires or measurements of nocturnal penile tumescence, the beneficial effects of testosterone replacement on both libido and erectile ability can be observed in a matter of weeks (Anderson et al, 1992). In an uncontrolled trial of HIV-infected men given testosterone enanthate up to 400 mg bi-weekly, self-ratings of sexual interest, erectile function and satisfaction with one's sex life were significantly improved (Wagner et al, 1997). Testosterone-treated patients also noted improvements in quality of life measures, as assessed by the Clinical Global Impressions Scale (Wagner et al, 1998).

Testosterone replacement improves the sense of well-being (Coodley and Coodley, 1997) and scores on the Beck Depression Index (SmithKline Beecham). In addition, testosterone replacement improves visuospatial abilities in hypogonadal young men (Janowsky et al, 1991).

Effects on body composition

The relationship of sex steroids to body composition is being actively studied. In animal models, androgen treatment increases protein synthesis and RNA polymerase (Krieg, 1976) activity in androgen-responsive tissues (Kochakian and Murlin, 1935). Replacement doses of testosterone increase lean body mass, muscle size and strength in healthy, young hypogonadal men (Brodsky et al, 1996; Katznelson et al, 1996; Bhasin et al, 1997) and older men with low testosterone levels (Tenover, 1992). Although other factors, such as exercise training, are undoubtedly involved, the treatment of healthy, eugonadal men with testosterone enanthate increases muscle mass and muscle protein synthesis, as measured by leucine uptake in muscle biopsy specimens (Griggs et al, 1989).

In healthy young men, pharmacological doses of testosterone enanthate (600 mg weekly) increased body weight, fat-free mass and maximum voluntary strength compared with placebo or exercise alone (Bhasin et al, 1996). The effects of supraphysiological doses of testosterone have not been examined in HIV-infected men.

The efficacy of testosterone replacement in HIV-infected men is not as clear. In an uncontrolled, open-label study, treatment of HIV-infected men who had lost weight before enrolment, with testosterone cypionate 400 mg bi-weekly, produced an average weight gain of 2.3 kg over 12 weeks. This included a 1.8 kg increase in body cell mass, with no change in body fat (Wagner et al, 1998).

Using 200 mg intramuscular testosterone enanthate, i.e. replacement doses, Coodley and Coodley (1997) did not detect an increase in weight. However, in another study, men randomized to 300 mg injectable testosterone every 3 weeks gained fat-free mass, lean body mass and muscle mass (Grinspoon et al, 1998).

Our group randomized 130 men who had lost a mean of 7% of their baseline weight to 6 mg testosterone administered by either a scrotal patch or a placebo patch. After 12 weeks of treatment, there were no statistical changes in weight, body composition or quality of life measures (Dobs, submitted for publication).

Bhasin et al (1998), however, were able to induce a 1.35 kg gain in lean body mass and a reduction in fat mass, compared with the placebo group, in HIV-infected, non-wasted men who were treated with a non-scrotal transdermal patch. In addition, subjects undergoing the active treatment showed an increase in red blood cell mass and an improvement in a measure of emotional stability.

Further studies are needed to examine the effects of specific testosterone preparations, doses and the resulting serum levels on weight gain in HIV-infected men.

Safety of testosterone therapy

Testosterone replacement therapy is generally safe. In hypogonadal men, testosterone replacement increases the prostate volume to a level seen in healthy, age-matched controls and is rarely associated with symptoms of prostatism (Behre et al, 1994). It is important to exclude men with prostate cancer. A digital rectal examination and a serum prostate specific antigen level should be measured in all men before initiating testosterone therapy.

Testosterone therapy, particularly when administered intramuscularly, increases haematocrit. In a smoker or someone living at a high altitude, testosterone administration may produce a greater increase in haemoglobin level; such men should be monitored closely to prevent polycythaemia. The exogenous administration of supraphysiological doses of androgens can cause a dramatic fall in serum high-density lipoprotein (HDL) level (Thompson et al, 1989). However, physiological testosterone replacement has only a minor effect on HDL level. Furthermore, testosterone therapy may decrease fat mass and improve insulin sensitivity (Marin et al, 1993). Therefore, we do not know the net effect of testosterone replacement on cardiovascular risk.

TESTOSTERONE FORMULATIONS

Parenteral administration of testosterone

Intramuscular injections of the testosterone esters enanthate and cypionate are commonly used for testosterone replacement therapy in hypogonadal men. The usual recommended dose is testosterone enanthate or cypionate 200 mg intramuscularly every 2 weeks. Pharmacokinetic studies reveal a peak serum level often into the supraphysiological range, 24 hours after the injection, the serum testosterone level then declines to the hypogonadal range at the end of the 2-week period. The administration of 100 mg hormone weekly can help to minimize fluctuations and maintain the serum testosterone level in the normal range. An alternative regimen is 300 mg every 3 weeks.

The advantages of parenteral forms include excellent absorption and lower costs, especially when men can give their own injections. With this method, patients can vary the dose of testosterone used. This would be useful if studies were to prove that there are advantages to using pharmacological doses of testosterone in certain disease states.

The disadvantages of intramuscular administration include the pain from the injection and the effects of the peaks and troughs of serum level. The latter has been termed a 'roller-coaster' effect and may be a problem in some men who experience irritability or anxiety with an elevated serum level and a sexual decline and depression at the end of the dosing interval. The supraphysiological testosterone level for several days after an injection increases the total exposure of androgen-sensitive tissues to this hormone.

Transdermal testosterone preparations

There are three transdermal preparations currently available in the USA. The first is a trans-scrotal testosterone delivery system called Testoderm, available in either 4 or 6 mg per day patches. The patches, placed on the scrotum daily, mimic a normal circadian rhythm, with peak serum testosterone levels 3–8 hours after application. During a 1-year study, 62% of men had a serum testosterone level over 12 mmol/l, 18% are between 10 and 12 nmol/l, and 20% are less than 10 mmol/l. Many hypogonadal men treated with the scrotal patch have a high serum dihydrotestosterone level because of the high 5α-reductase activity in scrotal skin (Winters and Atkinson, 1997). The scrotal patch offers men privacy but requires shaving of the scrotum weekly to improve patch adherence. The most common side-effects are itching (7%), discomfort (4%), local irritation (2%) and swelling (<1%).

The non-scrotal transdermal testosterone delivery system, Androderm, uses a permeation-enhancing vehicle containing ethanol, water, monoglycerides, fatty acid esters and gelling agents. One patch placed at night provides a nominal delivery of 5 mg testosterone over 24 hours. Absorption is best over flat skin, especially on the back, thigh, abdomen, upper arm and chest. In open-label, multicentre phase III trials, 92% of subjects achieved a normal morning testosterone level. The levels of oestradiol and dihydrotestosterone were within normal limits. The most common adverse event with the Androderm patch (53%) is skin irritation at the site of application. Of the 121 hypogonadal men treated with the Androderm patch, 12 patients (9.8%) discontinued therapy as a result of skin irritation. Pruritus (37%) and blister formation (12%) were less common.

A second non-genital patch, Testoderm TTS, has recently become available. This translucent patch produces a peak serum level in the region of 400 ng/dl. Using this patch, 18% of subjects complain of some skin irritation (ALZA Pharmaceuticals, Palo Alto, CA, USA).

Other formulations

Oral testosterone is not recommended for the treatment of hypogonadism because of the risk of cholestatic hepatitis, peliosis of the liver and hepatoma (Boyer et al, 1976). Testosterone undecenoate, a preparation available outside the USA, is an oral form of testosterone esterified to an unsaturated fatty acid that is absorbed through the intestinal lymphatics. It needs to be given three times daily since testosterone levels quickly fall to subtherapeutic ranges (Skakkebaek et al, 1981).

Long-acting injectable testosterone preparations have been used as male contraceptives rather than in the treatment of men with hypogonadism. Testosterone buciclate, 600 mg intramuscularly every 3–4 months, results in peak levels in 6 weeks (Behre et al, 1992).

Pellets of crystalline testosterone can be implanted subcutaneously into the abdominal wall. Plasma testosterone levels peak during the first month and gradually decline over 4–6 months. In non-HIV infected men, the risk

of bleeding and infection was less than 10% and less than 5% respectively (Handelsman et al, 1990).

Pharmacological doses of testosterone and other anabolic steroids

Testosterone analogues are often referred to as androgenic anabolics since they have effects on both the reproductive and somatic tissues (Rogozkin, 1979). The predominant effect on each of these tissues may vary between the steroids depending on such factors as residence time on the androgen receptor, binding to proteins and metabolism to other products. These compounds may be 19-methylated or 17-alkylated to permit oral administration. The specific chemical structure or dose of these derivatives needed to have an effect is not clear. Although athletes have used androgenic anabolics for decades in an attempt to increase muscle mass, the safety and efficacy of these compounds remains unclear.

Supraphysiological levels of testosterone can be attained by using higher doses of testosterone esters. Bhasin et al (1996) noted an increase in muscle mass in healthy men given testosterone enanthate 600 mg intramuscularly weekly, especially when used in conjunction with weight-lifting exercise. Similarly, in 31 healthy men, 200 mg testosterone enanthate given weekly for 8 weeks increased libido without changing overt sexual behaviour (Anderson et al, 1992).

In an uncontrolled study of HIV-infected men, supraphysiological doses of testosterone improved self-reported mood, energy, sexual behaviour and appetite, and were associated with an average 1.5 kg weight gain (Rabkin et al, 1995).

The effects of anabolic steroids on HIV-associated wasting are as yet unclear. Unfortunately, they are being used with increasing frequency, without long-term safety and efficacy data. Bucher et al (1996) reported an average weight gain of 1.5 kg in men receiving intramuscular injections of nandrolone decanoate 100 mg per week compared with placebo-treated men, who lost weight. There was no difference in the CD4 lymphocyte count or plasma mRNA HIV titre. In this study, the testosterone level decreased in the treatment group. In another open-label study using 100 mg nandrolone decanoate every 2 weeks, there was an increase in body weight, lean body mass and functional capacity (Gold et al, 1996).

Oxandrolone is an orally active, synthetic anabolic steroid that has been claimed to be 3–13 times more potent than testosterone in its anabolic effects (Blizzard et al, 1991). In a small study of placebo versus oxandrolone 5 and 15 mg per day in HIV-infected men, there was an increase in weight, appetite, strength and physical activity early in the study but no change in strength (Berger et al, 1996). By the end of 16 weeks, however, there were no statistically significant differences in weight between the groups. Clinical trials of higher doses are presently underway.

Oxymetholone, an oral preparation, has been reported to increase weight when used alone or in combination with ketotifen, an agent that decreases concentrations of tumour necrosis factor (Hengess, 1997). After 20 weeks of treatment, an average weight gain of 8.2 kg was observed in the

oxymetholone group and 6.1 kg in the combination group, compared with an average weight loss of 1.8 kg in the untreated control group. Lean body mass was not measured. The Karnofsky score of functional status increased significantly in the treated group at 20 weeks.

CONCLUSION

Hypogonadism occurs frequently during the course of HIV infection, particularly in HIV-infected men with wasting. In healthy hypogonadal men, testosterone replacement improves quality of life, sexual function, lean body mass and strength. However, we do not know whether physiological testosterone replacement can produce clinically meaningful changes in body composition and muscle function in HIV-infected men. If an HIV-infected man has a serum testosterone level below the normal range, it is reasonable to consider treatment with any of the testosterone preparations available, as would be done for a man without HIV infection.

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