Dihydrotestosterone

By Ronald Steriti, ND, PhD

© 2010

Dihydrotestosterone (DHT) is an androgen, synthesized primarily in the prostate gland, testes, hair follicles, and adrenal glands by the enzyme 5alpha-reductase (5-AR), which reduces the 4,5 double-bond of the hormone testosterone. There are two forms:

  - 5-alpha-DHT is an active metabolite of testosterone dependant upon the 5-alpha-reductase enzyme.
  - 5-beta-DHT is an active metabolite of testosterone dependant upon the 5-beta-reductase enzyme.

Although DHT is more potent that testosterone, only about 5% of serum testosterone produced in men undergoes 5α-reduction to form it. DHT has three times greater affinity for androgen receptors than testosterone and has 15-30 times greater affinity than adrenal androgens. (Wright, Thomas et al. 1996)

During embryogenesis DHT has an essential role in the formation of the male external genitalia, and in the adult DHT acts as the primary androgen in the prostate and hair follicles. Congenital 5-alpha-reductase deficiency results in male pseudohermaphroditism. (al-Attia 1997) (Hochberg, Chayen et al. 1996)

Metabolism

3-alpha and 3-beta-androstanediol (Adiol) are metabolites of 5-alpha dihydrotestosterone (DHT). These metabolites are dependant upon 3-alpha and 3-beta hydroxysteroid dehydrogenase (HSD) enzyme.

Figure 1: DHEA.jpg

Androgenic Alopecia

DHT is the primary contributing factor in androgenic alopecia (male pattern baldness).

Male pattern baldness is caused by a genetic sensitivity of hair follicles to DHT, which causes them to shrink when exposed to it. This shortens their
lifespan and prevents them from producing hair normally. (Hillmer, Hanneken et al. 2005)

Men with androgenic alopecia typically have higher levels of 5-alpha-reductase, lower levels of total testosterone, higher levels of unbound/free testosterone, and higher levels of total free androgens including DHT. (Starka, Cermakova et al. 2004) (Demark-Wahnefried, Lesko et al. 1997)

A recent study found that dihydrotestosterone inhibits murine hair growth via the androgen receptor. (Naito, Sato et al. 2008)

**Benign Prostatic Hyperplasia**

DHT plays a role in the development and exacerbation of benign prostatic hyperplasia, as well as prostate cancer, by enlarging the prostate gland. (Carson and Rittmaster 2003)

A recent study found that community dwelling men show a stepwise increase in benign prostatic hyperplasia risk with higher midlife serum dihydrotestosterone. (Parsons, Palazzi-Churas et al. 2010)

**Prostate Cancer**

It has been proposed that human prostatic adenocarcinoma depends on dihydrotestosterone and not testosterone for growth. (Petrow 1986)

Recent studies have found an association between low DHT and decreased survival in prostate cancer patients. (Nishiyama, Ikarashi et al. 2007) (Kjellman, Akre et al. 2008) (Nishiyama, Ikarashi et al. 2006)

One study found dihydrotestosterone levels decreased 91% in recurrent prostate cancer compared with androgen-stimulated benign prostate. (Titus, Schell et al. 2005)

Another study found an inverse relationship between tumor volume, as defined by PSA level, and 5 alpha-reductase activity, as defined by DHT level, and the testosterone/DHT ratio. (Gustafsson, Norming et al. 1996)

**The Estradiol-Dihydrotestosterone Model**

The Estradiol-Dihydrotestosterone (E-D) model proposes that 17beta-estradiol (E2) is essential for initiating the growth of prostate cancer cells through the formation of telomeres. It also proposes that testosterone is responsible for increasing the expression of proteins that cause apoptosis, or programmed cell death, and that 5alpha-dihydrotestosterone (DHT) is essential for preventing this. In addition, it is known that some testosterone is converted to both E2 and DHT, which means that depending on the conditions, testosterone is capable of either promoting the growth of or the killing of pancreatic cancer cells. (Friedman 2005)
Breast Cancer

The active estrogen estradiol (E2) stimulates breast cancer cell (BCC) growth, whereas the androgen dihydrotestosterone (DHT) has shown an antiproliferative effect. (Aka, Mazumdar et al. 2010)

Both 5 alpha-dihydrotestosterone and 5-androstene-3 beta,17 beta-diol stimulate proliferation of hormone-dependent cell lines at pharmacological levels via and interaction with the estrogen receptor. (Aspinall, Stamp et al. 2004)

Testosterone and 5 alpha-dihydrotestosterone inhibit in vitro growth of human breast cancer cell lines. (Ortmann, Prifti et al. 2002)

DHT stimulates, via the androgen receptor, the androgen-responsive breast cancer cells to produce a peptide factor(s) capable of inhibiting the growth of hormone-unresponsive cells. (Di Monaco, Leonardi et al. 1995)

DHT is a potent inhibitor of the stimulatory effect on E2 on cell proliferation, with the main action being related to a general increase in the duration of the cell cycle. (de Launoit, Dauvois et al. 1991)

17-beta HSD

Exposure to dihydrotestosterone (DHT) increased by 1.4-fold the reductive 17 beta HSD activity, the enzyme responsible for the inter-conversion of estrone (E1) and estradiol (E2). (Couture, Theriault et al. 1993)

Aromatase

One study showed that 5 beta-dihydrotestosterone inhibited of hypothalamic aromatase activity. (Schumacher, Hutchison et al. 1991)

An earlier study showed that DHT acts to increase aromatase activity in cultured fibroblasts by inducing the synthesis of new proteinaceous material. (Chabab, Sultan et al. 1986)

Growth Hormone


Dihydrotestosterone/Testosterone Ratio

A higher testosterone-to-dihydrotestosterone ratio was associated with a 42% decreased risk of benign prostatic hyperplasia when comparing the top 3 quartiles to the first quartile (OR 0.58, 95% CI 0.35-0.97, p = 0.04). (Parsons, Palazzi-Churas et al. 2010)
The dihydrotestosterone/testosterone ratio may be an important factor in the expression of androgenic activity, especially in the prostate. (Starka, Pospisilova et al. 2009)

One study examined dihydrotestosterone and testosterone levels in men screened for prostate cancer. The testosterone/DHT ratio tended to be higher in patients with more advanced tumors. There was an inverse relationship between tumor volume, as defined by PSA level, and 5 alpha-reductase activity, as defined by DHT level, and the testosterone/DHT ratio. This trend was most obvious with T-stage. (Gustafsson, Norming et al. 1996)

5alpha-Reductase Inhibitor Drugs

Dutasteride (Avodart) is approved for the treatment of BPH and is prescribed off-label for the treatment of MPB, whereas finasteride (Propecia) is approved for both conditions. (Aggarwal, Thareja et al. 2010) (Clark, Hermann et al. 2004)

In the Prostate Cancer Prevention Trial (PCPT), 25 percent fewer men taking the drug finasteride developed prostate cancer than men not taking the drug. However, men who developed prostate cancer while taking finasteride were more likely to have high-grade cancers, which can spread quickly even if the tumors are small. (Lucia, Epstein et al. 2007)

Dihydrotestosterone Therapy

5alpha-Dihydrotestosterone (DHT), the most powerful naturally occurring androgen, is commercially available since 1982 as a gel. DHT is used primarily in Europe. Unlike testosterone, it does not undergo any further amplification in potency through 5alpha reduction in the prostate. Secondly, it does not aromatize into estradiol. (Sakhri and Gooren 2007)

A study investigated the effects of dihydrotestosterone (DHT) gel on general well-being, sexual function, and the prostate in aging men. A total of 120 men participated in this randomized, placebo-controlled study (60 DHT and 60 placebo). DHT was administered transdermally for 6 months, and the dose varied from 125-250 mg/d. Early morning erections improved transiently in the DHT group at 3 months of treatment (P < 0.003), and the ability to maintain erection improved in the DHT group compared with the placebo group (P < 0.04). No significant changes were observed in general well-being between the placebo and the DHT group. Serum concentrations of LH, FSH, E2, T, and SHBG decreased significantly during DHT treatment. Hemoglobin concentrations increased from 146.0 +/- 8.2 to 154.8 +/- 11.4 g/liter, and hematocrit from 43.5 +/- 2.5% to 45.8 +/- 3.4% (P < 0.001). Prostate weight and prostate-specific antigen levels did not change during
the treatment. No major adverse events were observed. (Kunelius, Lukkarinen et al. 2002)

A double-blind, placebo-controlled, randomized clinical trial investigated the effects of transdermal dihydrotestosterone gel (70 mg for 3 months) on muscular strength, mobility, and quality of life in older men with partial androgen deficiency. Dihydrotestosterone had significant effects on circulating hormones (increased dihydrotestosterone; decreased total and free testosterone, LH, and FSH; unchanged SHBG and estradiol), lipid profiles (decreased total and low-density lipoprotein cholesterols; unchanged high-density lipoprotein cholesterol and triglycerides), hematopoiesis (increased hemoglobin, hematocrit, and red cell counts), and body composition (decreased skinfold thickness and fat mass; unchanged lean mass and waist to hip ratio). Muscle strength measured by isokinetic peak torque was increased in flexion of the dominant knee. (Ly, Jimenez et al. 2001)

Natural Therapies

Testosterone Replacement Therapy

A recent study found that plasma 5alpha-dihydrotestosterone (DHT) levels declined upon testosterone administration to elderly men with subnormal plasma testosterone and high DHT levels. (Gooren, Saad et al. 2008)

Zinc

Zinc arginine has been shown to be a 5 alpha-reductase inhibitor. (Fahim, Wang et al. 1993) (Sinquin, Morfin et al. 1982) (Grant, Minguell et al. 1971)

A study found that dietary zinc deficiency alters 5 alpha-reduction and aromatization of testosterone and androgen and estrogen receptors in rat liver. Hepatic conversion of testosterone to dihydrotestosterone was significantly less, but formation of estradiol from testosterone was significantly greater in rats fed the zinc-deficient diet compared with freely fed and pair-fed control rats. (Om and Chung 1996)

The effects of zinc therapy on plasma testosterone (T), dihydrotestosterone (DHT), and sperm count were studied in 37 patients with idiopathic infertility of more than five years duration. In the first group (T less than 4.8 ng/ml; 22 patients), T and DHT rose significantly after oral administration of zinc, as did the sperm count. Nine wives became pregnant, six within 3 months and three within 2 months of a second trial. In the second group (T greater than or equal to 4.8 ng/ml; 15 patients), T and sperm count were unaffected by zinc, while DHT increased significantly. (Netter, Hartoma et al. 1981)
Saw Palmetto

Saw Palmetto (Serenoa repens, Permixon) is an effective dual inhibitor of 5alpha-reductase isoenzyme activity in the prostate. (Habib, Ross et al. 2005) (Raynaud, Cousse et al. 2002)

Soy Isoflavones

One study showed that soy isoflavone supplements stimulated the production of serum equol and decreased the serum dihydrotestosterone levels in healthy male volunteers. A total of 28 Japanese healthy volunteers (18 equol producers and 10 equol non-producers) between 30 and 59 years of age were given soy isoflavones (60 mg daily) supplements for 3 months. No changes in the serum levels of estradiol and total testosterone were detected after 3-month supplementation. The serum levels of sex hormone-binding globulin significantly increased, and the serum levels of free testosterone and dihydrotestosterone (DHT) decreased significantly after 3-month supplementation. (Tanaka, Fujimoto et al. 2009)

An older study showed that soy protein, regardless of isoflavone content, decreased DHT and DHT/testosterone with minor effects on other hormones. Thirty-five men consumed milk protein isolate (MPI), low-isoflavone soy protein isolate (SPI) (low-iso SPI; 1.64 +/- 0.19 mg isoflavones/d), and high-iso SPI (61.7 +/- 7.35 mg isoflavones/d) for 57 d each in a randomized crossover design. Serum collected on d 1, 29, and 57 of each treatment revealed that dihydrotestosterone (DHT) and DHT/testosterone were significantly decreased by the low-iso SPI [9.4% (P = 0.036) and 9.0% (P = 0.004), respectively] and the high-iso SPI [15% (P = 0.047) and 14% (P = 0.013), respectively], compared with the MPI at d 57. Other significant effects included a decrease in testosterone by the low-iso SPI relative to the MPI (P = 0.023) and high-iso SPI (P = 0.020) at d 29; an increase in dehydroepiandrosterone sulfate by the low-iso SPI relative to the MPI at d 29 (P = 0.001) and relative to the MPI (P = 0.0003) and high-iso SPI (P = 0.005) at d 57; and increases in estradiol and estrone by the low-iso SPI relative to the MPI at d 57 (P = 0.010 and P = 0.005, respectively). (Dillingham, McVeigh et al. 2005)

Creatine Monohydrate

A double-blind placebo-controlled crossover study investigated resting concentrations of selected androgens after 3 weeks of creatine supplementation in male rugby players (n = 20). Subjects were loaded with creatine (25 g/day creatine with 25 g/day glucose) or placebo (50 g/day glucose) for 7 days followed by 14 days of maintenance (5 g/day creatine with 25 g/day glucose or 30 g/day glucose placebo). After 7 days of creatine loading, or a further 14 days of creatine maintenance dose, serum T levels did not change. However, levels of DHT increased by 56% after 7 days of
creatine loading and remained 40% above baseline after 14 days maintenance (P < 0.001). The ratio of DHT:T also increased by 36% after 7 days creatine supplementation and remained elevated by 22% after the maintenance dose (P < 0.01). (van der Merwe, Brooks et al. 2009)

**St John's wort**

St John's wort extract (SJW; Hypericum perforatum L.) is an herbal antidepressant.

A study found that the combined concentrations of the 5alpha-reduced steroids, androsterone sulfate and epiandrosterone sulfate, significantly declined following SJW treatment in all subjects (p = 0.02), and in males (p = 0.04). Furthermore, the testosterone to DHT ratio was increased in both men and women. Although the latter increase did not reach statistical significance, it is also consistent with the possible inhibition of 5alpha-reductase by SJW. (Donovan, DeVane et al. 2005)

**Tribulus terrestris**

Hormonal effects of Tribulus terrestris (TT) were evaluated in primates, rabbit and rat to identify its usefulness in the management of erectile dysfunction (ED). Tribulus extract was administered intravenously, as a bolus dose of 7.5, 15 and 30 mg/kg, in primates for acute study. Rabbits and normal rats were treated with 2.5, 5 and 10mg/kg of Tribulus extract orally for 8 weeks, for chronic study. In addition, castrated rats were treated either with testosterone cypionate (10mg/kg, subcutaneously; biweekly for 8 weeks) or Tribulus orally (5mg/kg daily for 8 weeks). Blood samples were analyzed for testosterone (T), dihydrotestosterone (DHT) and dehydroepiandrosterone sulphate (DHEAS) levels using radioimmunoassay. In primates, the increases in T (52%), DHT (31%) and DHEAS (29%) at 7.5mg/kg were statistically significant. In rabbits, both T and DHT were increased compared to control, however, only the increases in DHT (by 30% and 32% at 5 and 10mg/kg) were statistically significant. In castrated rats, increases in T levels by 51% and 25% were observed with T and Tribulus extract respectively that were statistically significant. Tribulus increases some of the sex hormones, possibly due to the presence of protodioscin in the extract. Tribulus may be useful in mild to moderate cases of ED. (Gauthaman and Ganesan 2008)

**Lignans**

Lignans interfere with 5 alpha-dihydrotestosterone binding to human sex hormone-binding globulin. (Schottner, Spiteller et al. 1998)
Adverse Effects of Drugs

Cyclosporine A

Nude mice treated with high doses of cyclosporine A had greater conversion of testosterone to 5 alpha-dihydrotestosterone, reflecting increased peripheral 5 alpha-reductase activity. (Boudou, Fiet et al. 1990)
References


