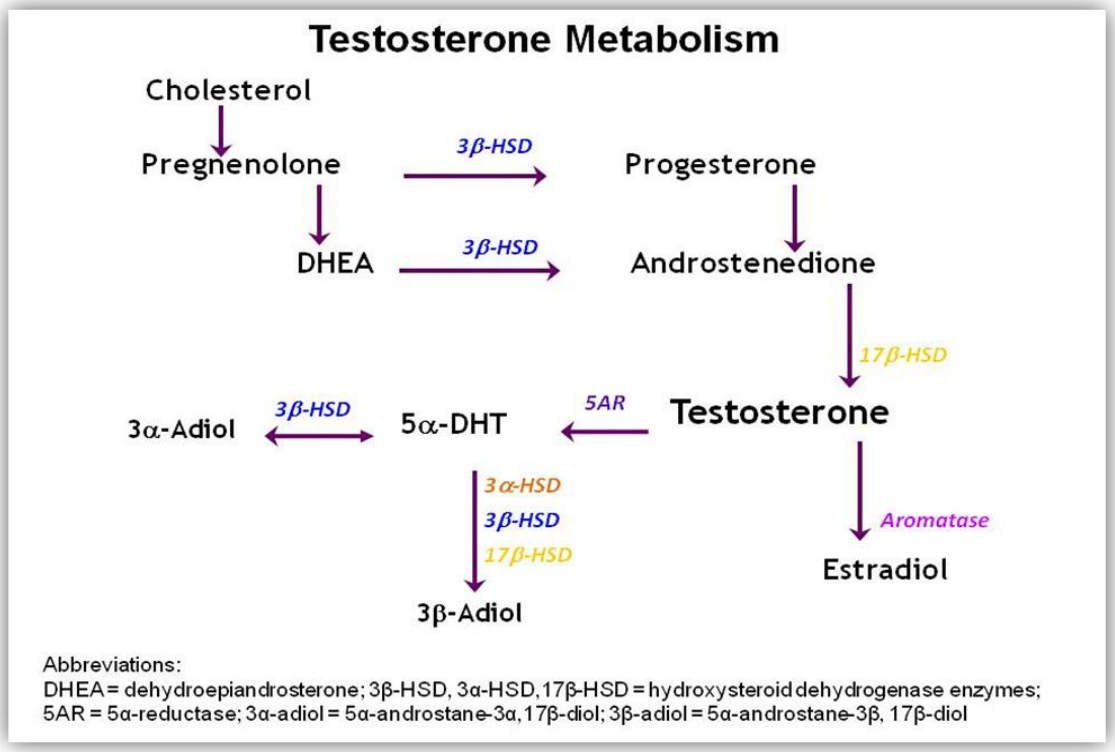
Clinical Significance of 5α-Reductase Activity

By Jonathan Wright, MD and Barry Wheeler, ND

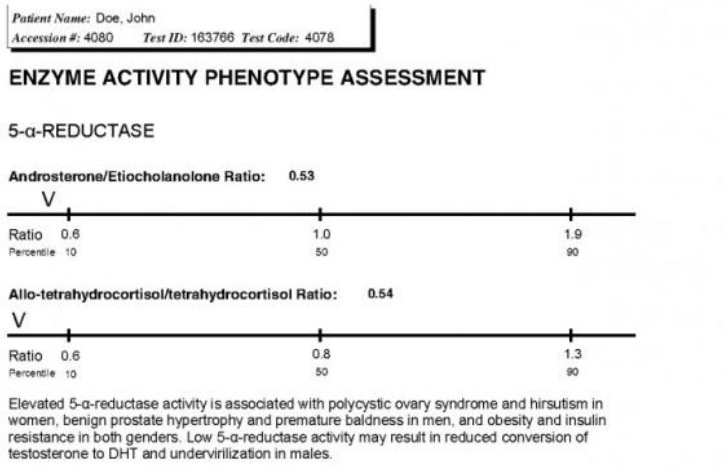


5α-Reductase (5AR) is the enzyme that catalyzes the conversion of (among others):

- Testosterone → 5α-DHT
- Androstenedione→ androsterone
- Cortisol → allo-tetrahydrocortisol

Measuring the levels of the above hormones and metabolites in urine and blood, we can quantify overall 5AR activity. In urine, two ratios are commonly used to assess 5AR activity:

- Androsterone : Etiocholanone
- Allo-tetrahydrocortisol : tetrahydrocortisol



Hormonal Regulation of 5AR

Dehydroepiandrosterone (DHEA) up-regulates 5AR activity.[1] Progesterone inhibits 5AR activity.[2] These two hormones can be easily and accurately assessed on a 24-hr urine hormone profile.

Increased 5α-Reductase Activity

Elevated 5AR activity is associated with obesity and insulin resistance in both men and women.[3] In women, increased 5AR activity is associated with polycystic ovary syndrome (PCOS) and hirsutism.[4] In men, elevated 5AR activity is associated with benign prostatic hypertrophy (BPH) and premature baldness.[4]

5-α Reductase Inhibitors

Some inhibition of 5AR may be desirable when 5AR activity is seen to be quite elevated. Natural 5AR inhibitors can provide effective moderate inhibition without shutting down 5AR altogether, which is seen with 5AR inhibiting drugs. Natural 5AR inhibitors include:

- Gamma-linolenic (GLA) , docosahexaenoic acid (DHA), and other fatty acids.[5,6]
- Serenoa repens (Saw palmetto)[7,8,9,10]
- Zinc [11,12]

Research on the effects of zinc on 5AR has shown that its inhibitory effects can be potentiated by vitamin B6. Supplements containing highly concentrated Saw Palmetto extracts may result in over-inhibition of 5AR. 5AR activity can be monitored in a 24-hour urine hormone profile.

Over-inhibition of 5AR decreases the production of dihydrotestosterone (DHT) resulting in increased levels of testosterone. The consequent aromatization of testosterone → estradiol may cause gynecomastia, a known side effect of 5AR inhibitor drugs.

Finasteride® and Dutasteride®

Patent medicines that inhibit 5AR are used to treat benign prostatic hyperplasia, prostate cancer, and baldness (androgenic alopecia). Two of these patent medicines are finasteride (Proscar®, Propecia®) and dutasteride (Avodart®). Currently, millions of men around the world take these drugs (as well as supplements mentioned above) to inhibit 5AR enzyme and decrease the production of 5α-DHT. There is evidence to suggest that one of the most potent inhibitors, finasteride, may cause residual impotence after discontinuation and possibly breast cancer in men.[13,14] Finasteride has been on the market since the early 1990s.

Risks of adverse drug reactions (ADRs) to 5AR inhibitors increase with dose. Common ADRs with these drugs include impotence, decreased libido, and decreased ejaculate volume. Rare ADRs include breast tenderness and enlargement, and allergic reaction.

Should We Inhibit Production of DHT?

While 5α-DHT has been implicated in male pattern baldness and benign prostatic hypertrophy, the real concern is prostate cancer. As early as 1986, it was suspected by some that 5α-DHT might be a primary contributing factor to prostate cancer growth.[15] 5α-Reductase (5AR) is responsible for conversion of testosterone to 5α-dihydrotestosterone (5α-DHT). 5α-DHT is about three times as potent as testosterone due to its greater affinity for androgen receptors.[16] However, recent studies have correlated low levels of DHT with *decreased* survival in prostate cancer patients.[17,18,19] Interestingly, a 2008 study found that giving testosterone to elderly men who had lower than normal levels of testosterone and elevated levels of DHT resulted in reduced plasma 5α-DHT levels.[20] Another study in 2007, a 15-yr follow up of men with prostate cancer, study shows evidence that low DHT is associated with decreased prostate cancer survival. [21]

Over-inhibition of 5α-Reductase Activity

While 5α-DHT is considered to be a potential cause of proliferation and growth in the prostate, its metabolite 5α-androstane-3β,17β-diol (3β-Adiol) is a differentiating agent that activates estrogen receptor beta (ERβ) and may help prevent cancer. Therefore, caution is warranted when inhibiting 5AR because without adequate DHT the production of 3β-adiol may be over-inhibited as well.[22]

Research regarding the benefits of adequate 3β-adiol is growing. 3β-adiol is an androgen that stimulates only estrogen receptor beta (ERβ), which has anti-proliferative and re-differentiation activities. Among other functions, ERβ helps regulate prostate growth and differentiation.[23,24,25,26] ERβ is also an important modulator of the stress

response in the brain.[27,28] Over-inhibition of 5AR can result in under-stimulation of ERβ, changing the balance of proliferative/anti-proliferative activity in the prostate and elsewhere.

Heavy metals, such as cadmium and arsenic, may also inhibit the production of 3β-adiol.[29,30] These heavy metals have been correlated with increased prostate cancer risks.

Another metabolite of 5α-DHT, 5α-androstane-3α,17β-diol (3α-Adiol), is a storage form for 5α-DHT and is easily "cycled back" to 5α-DHT.[28] At present, it appears that to get an accurate evaluation of "total" 5α-DHT levels (actual and potential) 3αAdiol and 5α-DHT should be added together.

Ratios are important

In the Rancho Bernardo study, a higher testosterone to DHT ratio was associated with a 42% decreased risk of BPH when comparing the top 3 quartiles to the first quartile (OR 0.58, 95% CI 0.35-0.97, p = 0.04). [31]

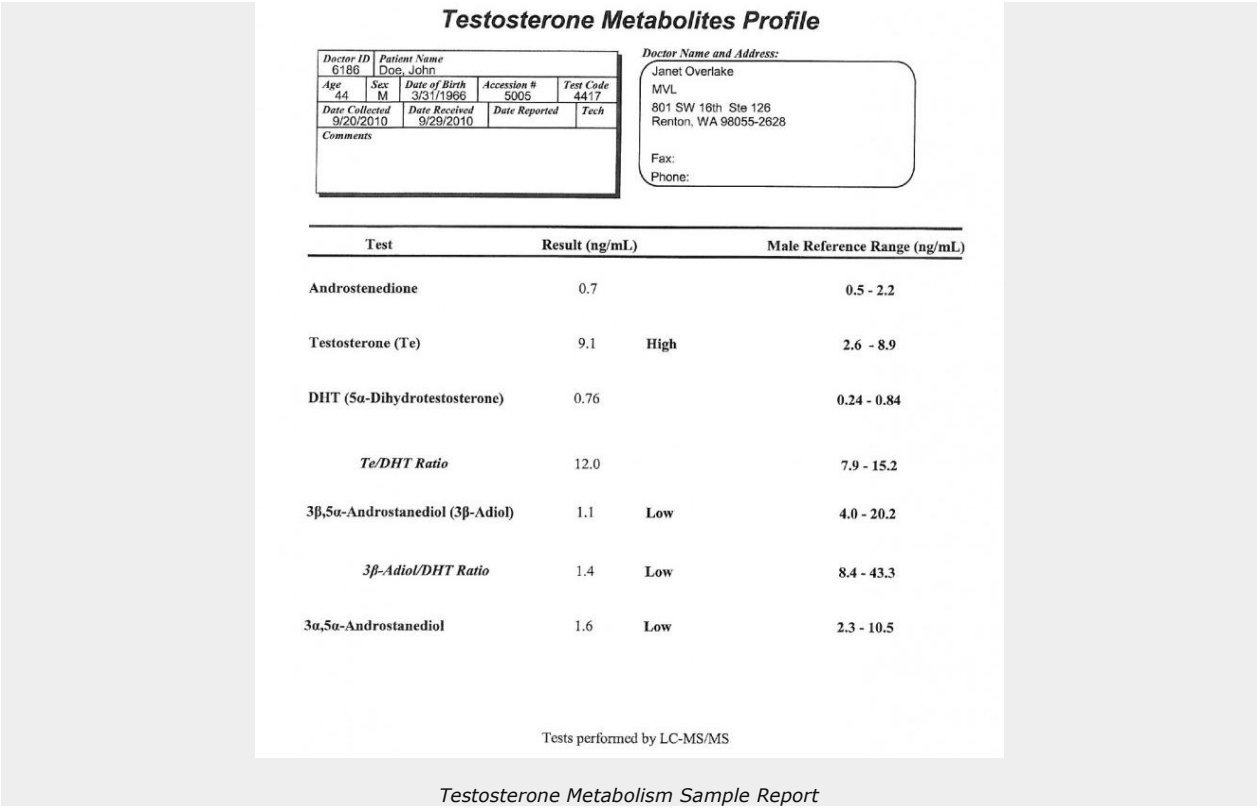
A 1996 study examined DHT and testosterone levels in men who were also screened for prostate cancer. The testosterone/DHT ratio tended to be higher in patients with more advanced tumors. There was an inverse relationship between tumor volume, as defined by PSA level, and 5AR activity. 5AR was defined by DHT level, and the testosterone/DHT ratio. This trend was most obvious with stage T-3.[32] T-stage refers to the level of spread in the prostate and surrounding tissues.

Testing for pro- and anti-proliferative metabolites

Very low levels of 5AR activity as expressed by ratios in urine hormone panels may indicate that the production of 5α-DHT is quite low. Consider follow-up testing with a serum Testosterone Metabolites Profile to assess the adequacy of 3β-Adiol production. Other patients who may benefit from evaluation of 3β-Adiol are those using 5AR inhibitors, having elevated testosterone or PSA, extremely high 5AR activity, or with a family history of prostate cancer.

This profile includes the following important ratios:

- Testosterone : 5α-DHT
- 3β-adiol: (5α-DHT + 3α-adiol)



Testosterone Metabolites Profile

Doctor ID	Patient Name			
6186	Doe, John			
Age	Sex	Date of Birth	Accession #	Test Code
44	M	3/31/1966	5005	4417
Date Collected	Date Received	Date Reported	Tech	
9/20/2010	9/29/2010			
Comments				

Doctor Name and Address:
Janet Overlake
MVL
801 SW 16th Ste 126
Renton, WA 98055-2628

Fax:
Phone:

Test	Result (ng/mL)		Male Reference Range (ng/mL)
Androstenedione	0.7		0.5 - 2.2
Testosterone (Te)	9.1	High	2.6 - 8.9
DHT (5α-Dihydrotestosterone)	0.76		0.24 - 0.84
Te/DHT Ratio	12.0		7.9 - 15.2
3β,5α-Androstanediol (3β-Adiol)	1.1	Low	4.0 - 20.2
3β-Adiol/DHT Ratio	1.4	Low	8.4 - 43.3
3α,5α-Androstanediol	1.6	Low	2.3 - 10.5

Tests performed by LC-MS/MS

Testosterone Metabolism Sample Report

As a leader in preventive medicine we are very interested in the growing body of evidence that the ratio of 5α-DHT to 3β-adiol may much more important than absolute levels alone. We are proud to be able to be the first and only lab to make testing for these testosterone metabolites commercially available. This test was developed by Dawn Huo, PhD and Ray Lian, PhD.

To learn more about Testosterone Metabolite Testing please visit MeridianValleyLab.com.

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