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Prostate tissue androgens: History and current clinical relevance

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Abstract

Direct determination of prostate tissue androgens, primarily dihydrotestosterone (DHT) and secondarily testosterone, can be performed on quick-frozen prostate biopsy cores or surgical specimens. Such assays have helped to clarify pathophysiology of BPH, prostate cancer chemoprevention, ‘escape’ of prostate cancer from hormonal control, safety of testosterone replacement therapy, and racial differences of prostate cancer. Future opportunities include clarification of new drug effects for BPH and prostate cancer, as well as a better understanding of the mechanisms of both, and as an aid in individual patient management. Determination of prostate tissue androgens may soon transition from research tool to clinical test.

INTRODUCTION

Androgenic activity in the prostate is a major mediator of tissue changes in the organ. However, compared to studies of circulating androgens, few studies of prostate tissue androgens are available, a major knowledge gap because circulating androgen levels may not reflect androgenic activity within the prostate gland¹⁻³. The purpose of this review is to call attention to the history and current clinical relevance of direct measurement of androgens in prostate tissue. Such determinations may soon transition from research tool to clinical test.

HISTORY OF PROSTATE ANDROGEN DETERMINATIONS

Huggins established the androgen-dependence of the prostate in the 1940s, but it was two discoveries of the 1960s that gave impetus for the study of prostate tissue androgens. The first was the radioimmunoassay (RIA), the Nobel-winning achievement of Yalow and Berson, providing for the first time a convenient method to quantify androgens and other hormones in body fluids¹. The method also proved applicable to quantification of *tissue* androgens². The second was the finding by Bruchovsky and Wilson that dihydrotestosterone

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(DHT), not testosterone, is the major androgen active within the prostate (Fig. 1)³. The distinction between testosterone, the prostatic pro-hormone, and DHT, the main effector androgen in the organ, was drawn soon thereafter by Imperato-McGinley et al in their studies of the Dominican ‘guevedoces’⁴. This discovery, which revealed that prostate size could be reduced without lowering testosterone levels in the systemic circulation, led to the development of finasteride, the first effective drug for treatment of men with symptomatic BPH.

From these fundamental discoveries---via studies of prostate tissue androgens---came a better understanding of the pathogenesis of BPH⁵; the first effective drug treatment of BPH⁶; a mechanism for the chemoprevention of prostate cancer (CaP)¹⁰; an explanation for the escape of CaP from castration therapy²; clarification of the prostate effects of testosterone replacement therapy¹; and insights into the cause of racial differences of CaP¹¹⁻¹³.

Table 1 shows the testosterone and DHT levels reported in benign prostate tissue by various authors, since the discovery that DHT is the major intra-prostatic androgen³.

DISCOVERIES EXPEDITED BY STUDY OF PROSTATE TISSUE ANDROGENS

Following are the major examples to date, where the study of prostate tissue androgens has materially helped to increase our understanding of prostate diseases:

Pathogenesis of BPH

Soon after the discovery that DHT is the primary intra-prostatic androgen³, a number of investigators reported an increased accumulation of DHT in the prostate to be the mechanism of clinical BPH^{7,8,9}. However, Walsh et al observed that in these reports fresh surgical specimens had been used for the BPH tissue, whereas autopsy specimens were used for the ‘normal’ control tissue. When Walsh employed fresh tissue for both, no difference in tissue DHT levels was found⁵. The ‘increased’ DHT levels in BPH were actually the result of factitiously low levels in the cadaveric specimens. Thus from this study of prostatic androgens evolved the current concept that DHT plays a permissive, rather than a transformative role in the development of BPH¹⁰. Importantly for subsequent investigations, the importance of quick-freezing tissue specimens to stop ongoing metabolism and enzymatic degradation became a basic concept.

Medical Treatment of BPH

Another area where analyses of prostate tissue androgens proved important was in determining the mechanism of the 5 alpha-reductase inhibitors (5ARI). The 5ARI finasteride, the first drug approved for treatment of men with symptomatic BPH, exerts a prostate-shrinking effect by inhibiting the formation of DHT within the organ⁶. While finasteride causes circulating levels of DHT to decline by some 70%, the drug causes prostatic tissue levels of DHT to decline even more dramatically (Fig. 2)¹¹. With dutasteride, a 5ARI more potent than finasteride, the changes are even more pronounced, resulting in almost complete elimination of prostatic DHT¹². A related effect of the 5ARI mechanism is a several-fold increase in prostatic tissue levels of testosterone (but only a slight increase in serum levels)¹¹; this tissue change may explain why castration has a much more profound

effect on the prostate than 5ARI¹³. Suppression of intra-prostatic DHT by early use of 5ARI in selected patients (ie, based on prostate volume and its surrogate, serum PSA levels) may help *prevent* complications of the enlarged prostate, ie, 'BPH disease'¹⁴.

Additionally, determinations of prostate tissue androgens have been used to test the hypothesis that saw palmetto extracts may exert a biological effect on the prostate. In a randomized, placebo-controlled trial employing a standardized saw palmetto compound, biopsies of the prostate were obtained at baseline and after six months of randomization in 40 men with symptomatic BPH¹⁵. When the biopsy samples were analyzed for tissue androgens, a mild, but statistically significant decrease in tissue DHT levels was observed in the saw palmetto group. Clinical benefit was not apparent in this trial, as it was not powered to detect changes in symptoms or urine flow, but by analyzing prostate tissue androgens, a possible mechanism of action for this popular herb was discerned.

Chemoprevention of Prostate Cancer (CaP)

Suppression of prostatic DHT also underlies the rationale for use of the 5ARI drugs finasteride and dutasteride in the prevention of CaP. These two drugs, particularly dutasteride, may be effective against early neoplastic changes in the prostate. Dutasteride has been shown to promote apoptosis and inhibit proliferation of LnCaP cells, suggesting a molecular basis for use of the drug in chemoprevention¹⁶. In men with localized CaP, pre-treatment with dutasteride resulted in atrophic changes and a shrinkage in tumor volume in their radical prostatectomy specimens, compared to that seen in placebo-treated controls¹⁷. Because CaP is commonly associated with overexpression of Type 1 5AR¹⁸, and because dutasteride inhibits both Type 1 and 2 5AR, the results of the REDUCE trial (Reduction by Dutasteride in Prostate Cancer Events) are awaited with interest¹⁹.

Mechanism of 'Androgen Independence' of CaP

An extremely important discovery---that androgen deprivation therapy (ADT) often does not completely deprive the prostate of androgenic stimulation²⁰---was recently revived. In 1984, Geller and colleagues reported that castration failed to completely eliminate intra-prostatic androgen levels in men with CaP²⁰. They concluded that the residual low, but measurable DHT levels were sufficient to stimulate tumor growth, and treatment strategies should be directed toward further inhibition of the AR signaling pathway. These findings were recently confirmed by the work of Mohler and associates²¹ and Nishiyama and colleagues²². Mohler's study was performed on tissue obtained by TURP in men with locally-advanced CaP who had received ADT for an average of 37 months; most men had rising PSA levels, and all 15 had castrate levels of serum testosterone. When androgen levels were determined on the resected prostate tissue, testosterone levels were only slightly lower than in the intact control group, and DHT levels, though substantially decreased, persisted at a level sufficient to activate the abundantly-present androgen receptor (AR). In a similar study from Nishiyama et al, prostate tissue DHT levels were reduced to ~25% of pre-treatment levels following 6 months of ADT, and there was no relationship between serum and tissue DHT levels²².

Importantly, in Mohler's patients, PSA was still actively being produced in the tissues of these androgen-deprived men with recurrent CaP. A similar finding was noted 2 decades earlier by Weber et al in BPH glands of men treated with medical castration during the 1980s (Fig 3A)²³. Moreover, the AR is virtually unaffected by ADT (Fig. 3B). In recent work by Page et al, medical castration for a month in healthy young men reduced prostatic androgens to 20-30% of control values and exerted little effect on prostatic apoptosis or epithelial cell proliferation²⁴. Castrate levels of testosterone in serum appear inadequate to prevent residual androgens in the prostate from stimulating androgen-regulated genes.

The implication of these tissue-androgen studies is that 'androgen-independent' CaP may actually be mediated by residual intra-prostatic androgens. In particular, residual DHT within the organ, remaining long after induction of systemic androgen deprivation, can activate the androgen receptor, which is essentially unaffected by ADT. Recent work by Mostaghel et al have corroborated and extended the Mohler and Nishiyama findings by showing that 9 months of ADT before radical prostatectomy did not suppress tissue levels of androgen-regulated genes encoding PSA and AR in the surgical specimen (Fig. 3C)²⁵. In fact, up-regulation of both AR and key enzymes for steroid biosynthesis in the prostate has been reported in men with 'androgen-independent' CaP²⁶.

Moreover, prostatic levels of androstenediol, the major metabolite of the adrenal androgen DHEA, are maintained after ADT at levels similar to that seen in the intact benign prostate; diol can stimulate the mutated AR directly, representing still another pathway for androgenic mediation of cancer in the gland despite castrate levels of circulating androgens²⁷. Stanbrough and colleagues have shown that the mechanism for the persistence of androgenic activity appears to be intra-prostatic conversion of adrenal steroids into testosterone and DHT²⁸. Further, Suzuki and colleagues recently demonstrated that adrenal androgen precursors are converted to DHT and induce metabolic activity (PSA secretion) in LnCAP cells²⁹.

The above tissue androgen studies have stimulated intense interest in finding new drugs to ablate residual prostatic androgens. In this regard, abiraterone, a C17,20-lyase inhibitor, which blocks synthesis of androgens just beyond cholesterol, is currently under investigation³⁰. The intra-prostatic potential of ketoconazole, a currently accepted second-line therapy for CaP, also warrants investigation. And, even more fundamentally, the androgen receptor *per se* remains an important direct therapeutic target³¹. The biology of the AR in 'androgen-independent' CaP has been reviewed recently by Scher and Sawyers³².

Testosterone Replacement Therapy (TRT) and the Prostate

Late-onset hypogonadism---formerly known as andropause, male menopause, and male climacteric---affects millions of men in the last third of life, constituting at present the main indication for testosterone administration (ie, TRT or testosterone replacement therapy)³³. However, because of the deleterious effect of testosterone in some men with advanced prostate cancer^{34,35}, and because of reports of CaP diagnosed in some men receiving TRT³⁶, prostate safety is the primary concern when aging men receive testosterone supplementation. In fact, Dr. von Eschenbach, the director of the U.S. FDA and previously a practicing urologist, told the *New York Times* in 2003, "Recognizing the dependency of prostate

cancer on testosterone, I am not convinced there is enough evidence on the safety of testosterone to justify its widespread use³⁷.”

The results of a clinical trial, focusing on prostate tissue androgens and conducted at the time of Dr. von Eschenbach’s statement, provide “Level 1 evidence” to lessen those fears³⁸. The trial was conducted to test the hypothesis that exogenous testosterone enters the prostate, is converted there to DHT, and causes biological change in the organ.

In this trial, 44 men with late-onset hypogonadism (and no CaP on baseline biopsy) were randomized 1:1 to receive placebo or parenteral testosterone (150 mg testosterone enanthate IM q2weeks) for six months in a double-blind fashion. The primary endpoints were prostate tissue levels of testosterone and DHT, which were determined by analysis of biopsy specimens obtained at baseline and after six months of randomization.

Key findings of the trial are shown in Fig. 4. While TRT normalized serum levels of testosterone, no change was seen in prostate tissue levels of testosterone or DHT. Further, no change was found in stroma-epithelial ratio, percent of atrophic glands, or in the major biomarkers for cell proliferation, angiogenesis, and AR. Further yet, no treatment-related effect on expression of androgen-regulated genes was found. At exit biopsy, small cancer foci were found in 4 of the men on placebo and in 2 men receiving TRT.

Establishment of prostate safety for large populations of aging men receiving TRT for long durations awaits the definitive study advocated by Cunningham, Bhasin, and others^{39,40}. However, from this focused study of prostate tissue androgens, we now have evidence that exogenous testosterone in doses sufficient to normalize serum levels does not accumulate in the prostate, does not produce abnormal levels of DHT, and does not induce any major biological change in the organ³⁸. Thus, the prostate risks to men undergoing TRT may not be as great as once believed. Apparently, the internal environment of the prostate is buffered against wide fluctuations in circulating androgen levels within a rather broad range (Fig. 5).

Racial Differences in Prostate Cancer (CaP)

Why CaP occurs more often and more severely in African-American men than in other men is not known, but racial differences in androgen levels have long been suspected as a factor.

Because no major racial differences in serum androgens are apparent, direct analyses of prostate tissue androgens has been used in at least 3 investigations of this subject. In 1988, a detailed study from Nigeria showed that black men there had prostatic androgen levels similar to those reported in Caucasian men elsewhere⁴¹. Mohler and colleagues found that black and white men undergoing radical prostatectomy had similar levels of testosterone and DHT in their transition zone; though androstendiol levels were higher in the African-American men⁴². They also found no major differences in androgen levels between peripheral and transition zone tissues. Mohler concluded that the racial differences in CaP could not be explained on the basis of differences in prostate tissue androgens⁴². Marks et al reached a similar conclusion, based on a study using needle biopsy specimens to compare peripheral zone androgens in a matched group of African-American and Caucasian men⁴³.

Androgen Levels in Prostate Cancer (CaP) vs Benign Hyperplasia (BPH)

The Nigerian men (above) with CaP had tumor levels of testosterone lower than in tissues of Nigerian men with BPH⁴¹, but Heracek et al recently reported that in Eastern European men (presumably Caucasians) cancerous prostates contain significantly higher levels of both testosterone and DHT than benign prostates⁴⁴. Comparing androgenic activity in CaP vs BPH tissue is an important subject for future study.

A NOTE ON METHODOLOGY

Three issues relating to methodology of determining prostate tissue androgens should be emphasized.

Importance of fresh frozen tissue

Once prostate tissue is removed from the body, enzymatic metabolism of DHT commences almost immediately. Walsh et al showed that within two hours of extracorporeal incubation at 37 degrees C, prostate tissue loses approximately 50% of the true level of DHT⁵. Instantaneous freezing with transfer and storage of prostate specimens to an environment that inhibits enzyme activity (e.g. -80 degrees centigrade) should be accomplished without delay.

Biopsy cores as tissue samples

Most studies of prostate androgens to date have employed large aliquots of surgical specimens to reduce sampling error (Table 1). However, surgical specimens preclude serial study. If tissue androgen measurements are to become clinical tools, potentially important in the evaluation of ongoing treatments wherein effects on prostate androgens are to be quantified, then a less invasive method of specimen collection is needed.

The satisfactory use of needle biopsy for this purpose was reported by Brunn and colleagues from Denmark in 1988⁴⁵. In current practice, a core from each side of the gland is taken and the two values averaged. In a study of sampling variability, when 10 cores were obtained randomly from whole prostates ex vivo, the coefficient of variation (C.V., SD/mean) for tissue DHT levels ranged from 0.23 to 0.61. Thus the C.V. was sizable, but the values were similar to those obtained by others using large surgical aliquots, and there was no overlap in values between intact men and men treated with 5ARI¹⁵. In intact men, testosterone and DHT levels are reported to be the same in peripheral and transition zone⁴².

Assay Performance

An off-the-shelf assay for determination of prostate tissue androgens is not yet commercially available, but several large national labs are considering offering one. The assay we have used involves (a) homogenization of quick frozen 18 ga biopsy cores, (b) separation of steroids using high-performance liquid chromatography with Sephadex LH-20 columns, and (c) radioimmunoassay. We and others have also used mass spectroscopy when low-level sensitivity is required⁴⁶⁻⁴⁸. Our RIA method is described in detail elsewhere¹⁵ and is based on established methods for determining sex steroid hormones in umbilical cord blood of fetal non-human primates⁴⁹.

FUTURE OPPORTUNITIES

Many current questions could be clarified via studies of prostatic androgens. Among the most important is the issue of residual androgens in the prostate after conventional ADT. The value of existing agents such as ketoconazole and new drugs such as abiraterone---in the ablation of residual prostatic androgens, after ADT or *de novo*---could be addressed directly in controlled trials. The prostate safety of new testosterone preparations such as parenteral undecanoate⁵⁰ could be studied. The putative selectivity of SARMs (selective androgen receptor modulators) could be evaluated by study of prostatic androgens⁵¹ and targets of the AR. Further studies into the pathogenesis and medical therapies of BPH, as well as novel therapies for prostate cancer, could also be enhanced by knowledge of prostate tissue androgens. An important issue that remains to be clarified concerns the issue of androgenic activity in cancer vs benign tissue. Future study of prostate tissue androgens should help clarify many important clinical concerns and direct new therapy for men with both benign and malignant prostate disease.

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Fig. 1.

Recovery of radioactivity from prostate tissue following intravenous (IV) administration of radio-labeled testosterone. Within one minute of IV administration, testosterone is taken up by the rat prostate and at least 90% of it is converted to other steroids, primarily DHT. Prostate epithelial cell nuclei (dark bars) and cytoplasm (open bars). This work established the primacy of DHT as the main androgen within the prostate. Modified from Bruchovsky and Wilson, 1969³.

Fig. 2.

Effect of finasteride, a 5 alpha reductase inhibitor, on prostate tissue androgens in man. As a result of blocking the conversion of testosterone to DHT within the organ, tissue levels of DHT decrease and tissue levels of testosterone increase. From McConnell, et al, 1992¹¹ with permission.

Fig. 3. Persistence of PSA and androgen receptor (AR) in 'androgen-deprived' prostate tissue.
A. H&E stain (left panel) and PSA stain (right panel) of prostate tissue in a man with BPH rendered castrate for 6 months with a GNRH analog; note intact epithelium (large arrow)

with active PSA production. Atrophic epithelium is also present (small arrow). From Weber, et al, 1989²³ with permission.

B. Androgen receptor (AR) stain of intact BPH tissue (left panel) and androgen-deprived prostate cancer tissue (right panel). Note abundant AR expression despite castrate serum levels of testosterone. From Mohler, et al, 2004²¹ with permission.

C. Expression of genes for androgen receptor (AR, left panel) and PSA (right panel) in prostate cancer tissue of intact men (placebo) and men on GNRH analog for 3-9 months (castrate). Vertical axis depicts mean fold change in transcript expression induced by castration relative to placebo as determined by qRT-PCR. Expression of these genes is little changed by ADT. From Mostaghel, et al, 2007²⁵ with permission.

Fig. 4.

Effects of testosterone replacement therapy on serum and prostate tissue androgens of men with late onset hypogonadism. Normalization of serum testosterone levels (upper panel) does not cause any significant change in prostate tissue androgens (lower panel). From Marks, et al, 2006³⁸ with permission.

Fig. 5. Chart depicting buffering of prostate tissue against wide fluctuations in serum testosterone levels. The internal environment of the prostate appears to be ‘protected’ against a broad range of circulating testosterone levels. Numbers on axes are hypothetical. Intra-prostatic changes beyond the extremes of a broad range of normal are the subject of ongoing investigations.

TABLE.

Testosterone and DHT Levels in Prostate Tissue

Author, yr, ref.	Mean value, ng/gm		Tissue Source	N	Analytic Method
	Testosterone	DHT			
Siiteri, 1970 ⁷	0.9	1.3	Autopsy	15	Isotope dilution
	0.9	6.0	Surgery	10	
Albert, 1976 ²	0.2	5.8	Surgery	6	Radioimmunoassay
Walsh, 1983 ⁵	1.2	5.1	Surgery	21	Radioimmunoassay
Salerno, 1988 ⁵²	0.4	4.5	Surgery	19	Mass spectroscopy
Osegbe, 1988 ⁴¹	0.5	4.9	Surgery	60	Radioimmunoassay
Forti, 1989 ⁵³	0.4	4.5	Surgery	19	Mass spectroscopy
*McConnell, 1992 ¹¹	0.2	3.2	Surgery	20	Radioimmunoassay
Shibata, 2000 ⁵⁴	0.2	3.9	Surgery	27	Mass spectroscopy
*Mohler, 2004 ⁴²	0.9	2.4	Surgery	30	Radioimmunoassay
Wurzel, 2006 ⁴⁷	0.1	3.2	Surgery	21	Mass spectroscopy
**Marks, 2006 ³⁸	0.9, 2.0	6.8, 8.2	Biopsy	40	Radioimmunoassay
Page, 2006 ²⁴	1.8	9.2	Biopsy	4	Radioimmunoassay
*#Heracek, 2007 ⁴⁴	0.5	1.3	Surgery	57	Radioimmunoassay

Survey limited to data on benign, untreated, adult human prostate tissue

* Converted from molar values

** PBO & Active groups at baseline

Medians