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Intraprostatic testosterone and dihydrotestosterone. Part II: concentrations after androgen hormonal manipulation in men with benign prostatic hyperplasia and prostate cancer

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Androgen deprivation therapy (ADT) and 5-α-reductase (5AR) inhibition are used in the treatment of men with advanced or metastatic prostate cancer and benign prostatic hyperplasia (BPH), respectively. These drugs exert their effect by lowering androgen levels in the serum and allegedly, the prostate gland. It is, however, unknown whether (increased) intraprostatic androgen levels are associated with the pathogenesis of BPH and with the initiation and progression of prostate cancer. Also, it is unclear whether intraprostatic dihydrotestosterone (DHT) levels correlate with a response to initial hormonal therapy or with patient outcome. These uncertainties have resulted from the finding that serum testosterone levels do not necessarily reflect those in the prostate gland. Intraprostatic DHT levels of men being treated with 5AR inhibition, of those treated with ADT for hormone-naive prostate cancer, and of those with castration-resistant prostate cancer are all altered in an equivalent manner because of hormonal manipulation. Increased knowledge of the mechanisms of the androgenic steroid pathways in prostatic diseases, with a special focus on intraprostatic androgen levels, may lead to treatment that is tailored to the needs of the individual patient, and probably to new therapeutic targets as well.

What's known on the subject? and What does the study add?
The male steroid hormone metabolism is an important target in the treatment of prostatic diseases. However, present literature is inconsistent about intraprostatic concentrations of steroid hormones and the role of intraprostatic steroid hormones in the arise and the course of prostatic diseases is yet to be determined.

Part II of this two-piece mini-review reviews the effect of medication that alters the male steroid hormone metabolism (i.e. 5-alpha reductase inhibitors, androgen deprivation therapy) on intraprostatic steroid hormone concentrations. Better knowledge of the intraprostatic steroid hormone concentrations might lead to more individualized treatment and even to new medical targets.

KEYWORDS

prostate, prostate cancer, finasteride, dutasteride, testosterone, dihydrotestosterone, androgen treatment

INTRODUCTION

It has long been recognized that androgenic activity is a major mediator of biological processes in the prostate. Early studies from the 1940s onwards reported that androgen deprivation therapy (ADT), by oestrogens (diethylstilbestrol [DES]) or by surgical castration, was able to lower serum testosterone levels resulting in a marked biochemical and clinical response in men with metastasized prostate cancer. Currently, ADT by LHRH-agonist treatment or by bilateral orchidectomy is the standard treatment in those with advanced or disseminated disease [1,2]. The finding that dihydrotestosterone (DHT) is the major androgen in the prostate led to the development of drugs that block the enzyme that is known to convert testosterone to DHT, 5-alpha-reductase (5AR). Multiple randomized studies initiated in the 1980s on 5AR inhibition in men with BPH showed a reduction of prostate volume, improvement in symptoms and peak urinary flow, and a reduction of the risk of acute urinary retention and BPH-related surgery. In these men, clinical benefits were obtained without lowering testosterone levels in the systemic circulation.

In Part I of the present review on intraprostatic testosterone and DHT assessment, the levels of the most powerful biologically active androgens are outlined in the normal adult prostate, in untreated BPH, and in prostate cancer.

Part II of the present review gives an overview of intraprostatic androgen levels in men who receive treatment that is known to interfere with the hypothalamic-pituitary-gonadal axis, e.g. ADT and 5AR-inhibition. Knowledge of the levels of intraprostatic androgens before and after hormonal manipulation might give more insight into the bio-availability of intraprostatic androgens, and into the cellular mechanisms that lead to the success of or the resistance to drug-initiated treatments.

5AR INHIBITION

ANDROGEN LEVELS AND 5AR INHIBITION IN BPH

McConnell *et al.* [3] reported on 69 men with BPH, who were scheduled for TURP, to determine the effect of finasteride, a

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TABLE 1 Testosterone and DHT concentrations after 5AR inhibition

Authors	n	Year	Pathology	Method of determination	5AR inhibition	Tissue DHT, ng/g tissue	Tissue, testosterone, ng/g tissue
McConnell *et al.* [3]	69	1992	BPH	RIA	Placebo	2.97	0.2
					Finasteride 1 mg	0.4§	1.25§
					Finasteride 100 mg	0.14§	1.69§
Norman *et al.* [4]	10	1993	BPH	RIA	Placebo	5.39	0.32
	9				Finasteride 1 mg	1.1§	2.2§
	8				Finasteride 5 mg	0.49§	2.4§
Span *et al.* [5]	7	1999	BPH	RIA	Placebo	4.38	0.53
	13				Finasteride 5 mg	1.39§	2.81§
Geller *et al.* [6]	10	1990	BPH	RIA	Baseline	4.5	0.17
					Finasteride 5 mg	0.30§	1.18§
Hill *et al.* [7]	15	1996	BPH	RIA	Placebo	3.54	0.92
	6				Finasteride 5 mg	0.68§	1.96§
Marks *et al.* [8]	15	2001	BPH	RIA	Placebo	4.9	1.5
	7				Finasteride	1.0§	3.6§
Habib *et al.** [9]	9	1997	BPH	RIA	Placebo	26.6	30.8
	19				Finasteride 5 mg	22.9	58.5§
Andriole *et al.*† [10]	18	2004	BPH	GC-MS	Placebo	6.18	0.12
	16				Dutasteride 5/10 mg	0.17§	0.25§
Wurzel *et al.*† [12]	21	2007	BPH	LC-MS	Placebo	3.23	0.092
	22				Dutasteride 0.5 mg	0.21§	2.54§
Rittmaster *et al.*† [11]	21	2008	BPH + Prostate cancer‡	GC-MS/LC-MS	Placebo	3.37‡	0.17
					Dutasteride 0.5 mg	–	–
	72				2 weeks	0.55§	1.72§
	71				1 month	0.33§	1.91§
	22				3 months	0.26§	2.80§
	25				4 months	0.23§	3.40§
Gleave *et al.*† [13]	14	2006	Prostate cancer	GC-MS	Placebo	3.3	0.07
	14				Dutasteride 0.5 mg	0.23§	3.4§
	13				Dutasteride 3.5 mg	0.039§	2.8§

**Measurement in dry weight. †Similar study group. ‡Pooled data of BPH and prostate cancer patients. §Statistically significant difference against baseline. Placebo = placebo tablet or 'no therapy'. Testosterone: 1 nmol/L = 28.8 ng/dL; 1 ng = 0.00347 nmol. DHT: 1 nmol/L = 29.0 ng/dL; 1 ng = 0.00344 nmol. 5ARI, 5AR inhibitor; RIA, radioimmunoassay; LC, liquid-chromatography mass spectrometry; GC, gas-chromatography mass spectrometry.*

5AR-type-2 inhibitor, on clinical outcome, side-effects and (intraprostatic) androgen levels. Patients were treated with placebo or 1, 5, 10, 50 or 100 mg finasteride for 7 days before surgery. In the placebo group, the mean prostatic DHT level was 2.97 ng/g tissue, and the mean tissue testosterone level was 0.2 ng/g tissue (Table 1 [3–13]). There was an incremental increase of intraprostatic testosterone level and a reciprocal decrease of intraprostatic DHT level with higher dosages of finasteride. All treatment groups were significantly different from the placebo group, but not different from each other.

Norman *et al.* [4] studied 27 men who were scheduled for TURP for BPH and who were randomized between placebo ($n = 10$), and 6–8 weeks pretreatment with 1 mg finasteride ($n = 9$), or 5 mg finasteride ($n = 8$). Tissue DHT levels in the placebo group were 5.39 ng/g tissue, and decreased to 1.1 ng/g tissue for 1 mg finasteride, and 0.49 ng/g tissue for 5 mg finasteride ($P = 0.049$ between doses). Intraprostatic testosterone levels in the placebo group increased from 0.32 ng/g tissue to 2.2 ng/g tissue with 1 mg finasteride and 2.4 ng/g tissue with 5 mg finasteride ($P =$ nonsignificant between doses).

Similar decreases in intraprostatic DHT levels, and reciprocal rises of prostatic testosterone levels after finasteride treatment up to 100 mg/day have been reported by other study groups [5–8]; however, Habib *et al.* [9], in their randomized study on intraprostatic androgen levels on 5AR treatment, were unable to show a significant difference in testosterone and DHT levels between the finasteride and placebo-treated group.

Rittmaster *et al.* [10] published a study on intraprostatic androgen levels in men with BPH who were scheduled for TURP [10–12].

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Patients were randomized between surgery alone and placebo or neoadjuvant dutasteride, a dual 5AR-type-1 and -2 inhibitor, 0.5 mg or 3.5 mg. After 4 months of drug treatment, the mean intraprostatic DHT level was suppressed by 93.1% for 0.5 mg dutasteride and by 98.9% for 3.5 mg dutasteride (both $P < 0.001$ versus placebo). For testosterone, intraprostatic values were significantly greater in subjects who received dutasteride 0.5 mg or 3.5 mg versus the surgery-alone group ($P < 0.001$).

ANDROGEN LEVELS AND 5AR INHIBITION IN PROSTATE CANCER

Gleave *et al.* [13] performed a randomized study enrolling 75 men with clinically localized prostate cancer. Men enrolled in this study had biopsy-proven, clinically organ-confined prostate cancer with a Gleason score ≤7. Patients underwent radical prostatectomy and received either placebo, dutasteride 0.5 mg or 3.5 mg during a 4-month period before surgery. In the resected tissue, intraprostatic concentrations of DHT were 3.3 ng/g tissue for placebo, 0.23 ng/g tissue for 0.5 mg dutasteride and 0.039 ng/g tissue for 3.5 mg dutasteride ($P < 0.001$). Intraprostatic testosterone levels were significantly higher in subjects who received dutasteride 0.5 mg (3.4 ng/g tissue) and dutasteride 3.5 mg (2.8 ng/g tissue) vs the surgery-only group (0.07 ng/g tissue; $P < 0.001$ [Table 1]).

ANDROGEN LEVELS AND SAW PALMETTO IN BPH

Saw palmetto (*Serenoa repens*) is widely used in the treatment of men with a variety of urinary tract problems. The mechanism of action is unknown, but it has been suggested that the herb functions as a 5AR inhibitor. Forty-four men with symptomatic BPH were entered into a 6-month randomized trial of saw palmetto vs placebo [8]. Intraprostatic DHT levels were assessed in prostate biopsy cores at baseline as well as after 6 months of treatment. Within 20 evaluable patients on saw palmetto, there was a 32% modest but significant decline in intraprostatic DHT level from 6.49 ng/g tissue at baseline to 4.40 ng/g tissue at 6 months of treatment ($P < 0.005$). These results are compatible with, but not proof of the claimed 5AR inhibitory function of saw palmetto. Similar observations were made by Di Silverio *et al.* [14].

ADT

ANDROGEN LEVELS AND ADT IN BPH

Various types of ADT, alone or in combination, were compared for their effect on intraprostatic DHT concentration in patients with BPH. In studies by Geller *et al.* [15] and Geller and Albert [16], patients with BPH undergoing TURP were pretreated with various placebo-controlled androgen deprivation regimens consisting of the anti-oestrogen tamoxifen ($n = 7$), the AR-antagonist flutamide ($n = 12$), the progestogen megestrol-acetate ($n = 23$), DES, ketoconazole, or combinations thereof. Within the untreated group, the reference intraprostatic DHT concentration was 6.0 ng/g tissue. For the androgen deprivational regimens, mean values for tissue DHT were 5.83 ng/g tissue for tamoxifen, 3.89 ng/g tissue for flutamide, and 1.37 ng/g tissue for megestrol-acetate (Table 2 [15–24]). Megestrol-acetate combined with tamoxifen showed a tissue DHT concentration of 1.77 ng/g tissue ($n = 6$), the combination of megestrol- acetate and DES 0.81 ng/g tissue ($n = 10$), and the combination of megestrol-acetate and ketoconazole ($n = 4$) 0.74 ng/g tissue. All groups, except for tamoxifen, showed a significantly lower intraprostatic DHT level compared with placebo ($P < 0.01$).

Forti *et al.* [17] found that intraprostatic DHT levels in men treated with an LHRH agonist before open prostatectomy for BPH were about 10% of those who were untreated, i.e. 0.48 ng/g tissue vs 4.49 ng/g tissue, respectively ($P < 0.01$). Intraprostatic testosterone levels in the treated men (0.106 ng/g tissue) was about 25% of those in the untreated group (0.404 ng/g tissue; $0.10 > P > 0.05$). In tissues with low 5AR activity (renal and uterine tissue), tissue testosterone concentrations were significantly higher than in the prostatic tissue of LHRH agonist-treated men. Interestingly, even if only one tenth of the level of untreated men, DHT levels in LHRH-treated men were still higher than those in renal and uterine tissue.

Page *et al.* [18] showed that prostate tissue DHT levels in healthy volunteers decreased by 80% after 1 month of LHRH antagonist treatment and that intraprostatic androgen levels were not suppressed to the same degree as serum androgen levels.

ANDROGEN LEVELS AND ADT IN PROSTATE CANCER

Multiple studies have shown that relatively large amounts of DHT exist in prostate cancer tissue after (surgical) castration in humans [19,20]. To assess the effect of ADT on intraprostatic concentrations of androgens in prostate cancer, Nishiyama *et al.* [21] performed an analysis of 30 patients with biopsy-proven, clinically localized prostate cancer. These patients were given an LHRH agonist (or underwent bilateral orchiectomy) in a neoadjuvant settting for 6 months before radical prostatectomy. Intraprostatic DHT levels before treatment were 5.44 ng/g tissue and declined to 1.35 ng/g tissue after 6 months of ADT (i.e. 25% of baseline [$P < 0.001$]). Serum testosterone, serum DHT and tissue DHT levels showed no significant difference between patients with Gleason score 7–10 and Gleason score 6 prostate cancer before and after ADT [22].

ANDROGEN LEVELS AND ADT IN CASTRATION-RESISTANT PROSTATE CANCER

Mohler *et al.* reported on tissue androgen levels in 15 men with castration-resistant prostate cancer (CRPC; Gleason scores 8–10) [23]. For comparison, benign prostate tissue samples were obtained from 16 patients treated for LUTS by TURP. None of these men received androgen treatment before surgery. Tissue levels of testosterone were similar in recurrent prostate cancer (0.80 ng/g tissue) and benign prostate tissue (0.95 ng/g tissue; $P = 0.21$), whereas tissue levels of DHT were 82% lower in CRPC (0.42 ng/g tissue) than in the benign prostate (2.36 ng/g tissue; $P < 0.01$ [Table 2]).

Similar observations were made by Titus *et al.* [24] comparing tissue testosterone and DHT levels in 18 men with CRPC to those in 18 men with BPH and no previous hormonal treatment. Testosterone levels were similar in recurrent prostate cancer (1.09 ng/g tissue) and BPH (0.80 ng/g tissue), whereas DHT levels decreased by 91% in recurrent

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TABLE 2 Testosterone and DHT concentrations after ADT

Authors	n	Year	Pathology	Method of determination	ADT	Tissue DHT, ng/g tissue	Tissue testosterone, ng/g tissue
Page *et al.* [18]	4	2006	normal prostatic tissue	RIA	Placebo	9.3	1.8
	4				LHRH antagonist	1.9¶	0.4§
	4				LHRH antagonist + testosterone gel	6.8	1.2
Geller *et al.* [15]*	6	1976	BPH	RIA	No treatment	3.9	
	6				MA	1.1¶	
Geller *et al.* [16]*	25	1987	BPH	RIA	No treatment	6.00	
	7				Tamoxifen Flutamide MA	5.83	
	12					3.89¶	
	23					1.37¶	
	6				MA + tamoxifen	1.77¶	
	10				MA + DES	0.81¶	
	4				MA + ketoconazol	0.74¶	
Forti *et al.* [17]	19	1989	BPH	GC-MS	No treatment	4.49	0.404
	7				LHRH agonist	0.48¶	0.106¶
Belanger *et al.* [20]	5	1989	Prostate cancer	RIA	Surgical castration	2.7	
	4				Surgical castration + flutamide	<0.3¶	
Mizokami *et al.* [19]	12	2004	Prostate cancer	LC-MS/MS	LHRH agonist + anti-androgen	0.619	
Nishiyama *et al.* [21]†	8	2004	Prostate cancer	LC-MS	Before treatment	5.44	
	22					1.69¶	
					Surgical castration or LHRH agonist + flutamide	1.23¶	
Nishiyama *et al.* [22]†	28	2007	Prostate cancer	LC-MS	Surgical castration	1.3	
	18		Gleason ≤6		or LHRH agonist	1.0	
	10		Gleason ≥7		+/– flutamide	1.9	
Mohler *et al.* [23]‡	15	2004	CRPC	RIA	Medical or surgical castration	0.42	0.80
Titus *et al.* [24]‡§	18	2005	CRPC	LC-MS/MS	ADT	0.36	1.09

**Similar study group. †Similar study group. ‡Similar study group. §Levels are medians. ¶Statistically significant difference against baseline. Testosterone: 1 nmol/L = 28.8 ng/dL; 1 ng = 0.00347 nmol. DHT: 1 nmol/L = 29.0 ng/dL; 1 ng = 0.00344. nmol. RIA, radio immunoassay; LC, liquid-chromatography mass spectrometry; GC, gas-chromatography mass spectrometry; MA, megestrol-acetate.*

prostate cancer (0.36 ng/g tissue) compared with BPH (3.98 ng/g tissue; $P < 0.001$).

ANDROGEN LEVELS IN PATIENTS WITH LATE ONSET HYPOGONADISM

Serum levels of testosterone are known to decline with age, and in many aging men with low levels of testosterone a constellation of symptoms develops that is referred to as late onset hypogonadism (LOH). If the severity of these complaints is very great, testosterone replacement therapy (TRT) is considered. A primary concern in aging men who receive TRT is 'prostate safety', the possibility of initiating or stimulating growth of prostate cancer (or BPH).

Marks *et al.* [25] published a study on 40 men with LOH, who were randomized between 150 mg testosterone i.m. for 6 months or placebo. After 6 months of treatment, concentrations of androgens in serum and prostatic tissue were assessed. Prostate biopsy was performed in all to see if TRT caused histological changes in the prostate. In the treated group, serum testosterone levels increased from 282 ng/dL to 640 ng/dL with no significant change in testosterone levels in the placebo-treated group. The reported intraprostatic testosterone levels were 0.91 ng/g tissue at baseline and 1.55 ng/g tissue at 6 months of TRT, whereas intraprostatic DHT levels were 6.79 ng/g at baseline and 6.82 ng/g after treatment (both nonsignificant). Also, no treatment-related change was observed in prostate histology (i.e. occurrence of prostate cancer) after 6 months of TRT. These data suggest that testosterone treatment appears to have little effect on intraprostatic androgen levels and does not cause any major biological change (such as carcinogeneity) in the prostate in men with LOH, although it should be noted that this trial involved a small number of participants and had a relatively short follow-up.

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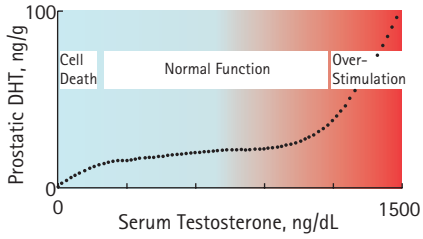
FIG. 1. Buffering of prostate tissue against wide fluctuations in serum testosterone levels. The internal environment of the prostate appears to be 'protected' against a broad range of circulating testosterone levels. Numbers on axes are hypothetical. Reproduced with permission from Elsevier Inc. [8]



DISCUSSION

It is widely recognized that the prostate is an androgen-dependent organ. Normal prostatic development requires not only testosterone, but also the activity of 5AR, an enzyme that converts testosterone to the more biologically active androgen DHT. ADT by surgical castration, or by drugs that block the hypothalamic-pituitary-gonadal axis lowers serum testosterone to ≈10% of that of baseline, and consequently, androgen ablation has become the first-line treatment in patients with advanced or disseminated prostate cancer. The relationship between serum testosterone and prostate cancer (aggressiveness), however, is poorly understood. The conflicting findings about the association between serum testosterone levels and features of prostate cancer (or, clinical BPH) suggest that local factors within the prostate may be involved.

The prostate expresses high levels of steroid-converting enzymes such as 5AR type 2, and therefore endocrine activity in the prostate gland may differ substantially from that in serum and other organs. Is should be kept in mind that methodological differences exist that make comparisons of intraprostatic androgen levels between research groups difficult [26]. Serum and intraprostatic testosterone levels have been reported to substantially increase after 5AR- inhibitory treatment [10–13], with a reciprocal and more pronounced decrease in intraprostatic DHT levels (Table 1). In men treated for BPH, intraprostatic DHT levels after 5AR inhibitory treatment (finasteride 1–100 mg or dutasteride 0.5–3.5 mg) decreased >80% overall, with a more substantial reduction (>90%) of intraprostatic DHT level for 0.5 mg dutasteride [3–13]. Near complete reductions in DHT levels (>95%) have been observed in prostate cancer tissue in men treated with dutasteride 0.5 mg and dutasteride 3.5 mg before radical prostatectomy [11,13].

Despite the demonstration of castration levels of testosterone in serum, different studies have shown that treatment of prostatic disease with ADT does not reduce intraprostatic androgen concentrations to undetectable levels [15–24]. Intraprostatic DHT concentrations in men who have been surgically or medically castrated are maintained at a level ≈10–40% of the level in benign prostatic tissue. Intriguingly, intraprostatic DHT levels in men being treated with 5AR inhibition for signs and symptoms related to BPH do not differ substantially from those of men being treated with ADT for hormone-naïve (advanced or metastatic) prostate cancer or men with recurrent prostate cancer treated by ADT (Tables 1,2). The reported DHT levels in all three patient groups described are well above the levels required to activate the androgen receptor based on studies in prostate cancer cell lines [27,28]. Levels above the minimal activation threshold do not appear to contribute to additional gene expression activity [25]. Apparently, the androgen-regulated biological functions in the prostate are buffered against wide fluctuations in circulating androgens (Fig. 1). In addition, testosterone administration (even in extreme dosages) has not led to malignant neoplasia in primate or canine studies. Suppletion of testosterone in men with LOH has not been shown to increase androgen levels in the prostate. While serum levels of testosterone and DHT (and oestradiol) increase after TRT, no evidence of an increased incidence of BOO attributable to prostate enlargement or an increased incidence of prostate cancer have been reported [25].

In conclusion, ADT and 5AR inhibition are now used in the treatment of men with advanced or metastatic prostate cancer and BPH, respectively. These drugs are aimed at lowering androgen levels in the serum and prostate gland; however, it is not known whether (increased) intraprostatic androgen levels are associated with the pathogenesis of BPH and with the initiation and progression of prostate cancer. It is unclear whether intraprostatic DHT levels correlate with clinical responsiveness to firstly initiated hormonal therapy or with patient outcome. These uncertainties have resulted from the finding that serum testosterone levels do not reflect those in the prostate gland. Different hormonal manipulations in men with either BPH or prostate cancer alter intraprostatic DHT levels equally. Increased knowledge of the mechanisms of the androgenic steroid pathways in prostatic diseases, with a special focus on intraprostatic androgen levels, may lead to treatment that is tailored to the needs of the individualized patient, and probably to new therapeutic targets as well. New agents such as CYP17-inhibitors and the anti-androgen MDV3100 indeed aim at altering the intraprostatic androgen metabolism. At last, the availability of more reliable and accurate means to measure serum- and intraprostatic androgen levels (reviewed in Part I) may give more insight into the pathomechanism of BPH and prostate cancer, and in the sequelae of medical interference as well.

CONFLICT OF INTEREST

None declared.

REFERENCES

1 **Soloway MS, Chodak G, Vogelzang NJ *et al*.** Zoladex versus orchiectomy in treatment of advanced prostate cancer: a randomized trial. Zoladex Prostate Study Group. *Urology* 1991; **37**: 46–51
2 **Peeling WB.** Phase III studies to compare goserelin (Zoladex) with orchiectomy and with diethylstilbestrol in treatment of prostatic carcinoma. *Urology* 1989; **33** (5 Suppl.): 45–52
3 **McConnell JD, Wilson JD, George FW *et al*.** Finasteride, an inhibitor of 5 alpha-reductase, suppresses prostatic dihydrotestosterone in men with benign prostatic hyperplasia. *J Clin Endocrinol Metab* 1992; **74**: 505–8
4 **Norman RW, Coakes KE, Wright AS, Rittmaster RS.** Androgen metabolism in men receiving finasteride before prostatectomy. *J Urol* 1993; **150**: 1736–9
5 **Span PN, Voller MC, Smals AG *et al*.** Selectivity of finasteride as an in vivo

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inhibitor of 5- alpha reductase isoenzyme activity in the human prostate. *J Urol* 1999; **161**: 332–7
6 **Geller J.** Effect of finasteride, 5 alpha reductase inhibitor on prostate tissue androgens and prostate-specific antigen. *J Clin Endocrinol Metab* 1990; **71**: 1552–5
7 **Hill M, Petrik R, Hampl R *et al*.** The concentrations of the endogenous C19-steroids in hyperplastic prostatic tissue and the effects of finasteride treatment. *Horm Metab Res* 1996; **28**: 562–4
8 **Marks LS, Hess DL, Dorey FJ *et al*.** Tissue effects of saw palmetto and finasteride: use of biopsy cores for in situ quantification of prostatic androgens. *Urology* 2001; **57**: 999–1005
9 **Habib FK, Ross M, Tate R *et al*.** Differential effect of finasteride on the tissue androgen concentrations in benign prostatic hyperplasia. *Clin Endocrinol* 1997; **46**: 137–44
10 **Rittmaster R, Hahn RG, Ray P *et al*.** Effect of dutasteride on intraprostatic androgen levels in men with benign prostatic hyperplasia or prostate cancer. *Urology* 2008; **72**: 808–12
11 **Andriole GL, Humphrey P, Ray P *et al*.** Effect of the dual 5-alpha reductase inhibitor dutasteride on markers of tumor regression in prostate cancer. *J Urol* 2004; **172**: 915–9
12 **Wurzel R, Ray P, Major-Walker K *et al*.** The effect of dutasteride on intraprostatic dihydrotestosterone concentrations in men with benign prostatic hyperplasia. *Prostate Cancer Prostatic Dis* 2007; **10**: 149–54
13 **Gleave M, Qian J, Andreou C *et al*.** The effects of the dual 5alpha-reductase inhibitor dutasteride on localized prostate cancer–results from a 4-month pre-radical prostatectomy study. *Prostate* 2006; **66**: 1674–85
14 **Di Silverio F, Monti S, Sciarra A *et al*.** Effects of long-term treatment with serenoa repens (Permixon ©) on the concentrations and regional distribution of androgens and epridermal growth factor en benign prostatic hyperplasia. *Prostate* 1998; **37**: 77–83
15 **Geller J, Albert J, Geller S *et al*.** Effect of megestrol acetate (Megace) on steroid metabolism and steroid-protein binding in the human prostate. *J Clin Endocrinol Metab* 1976; **43**: 1000–8
16 **Geller J, Albert J.** Effects of castration compared with total androgen blockade on tissue dihydrotestosterone (DHT) concentration in benign prostatic hyperplasia (BPH). *Urol Res* 1987; **15**: 151–3
17 **Forti G, Salerno R, Moneti G *et al*.** Three-month treatment with a long-acting gonadotropin- releasing hormone agonist of patients with benign prostatic hyperplasia: effects on tissue androgen concentration, 5 alpha-reductase activity and androgen receptor content. *J Clin Endocrinol Metab* 1989; **68**: 461–8
18 **Page ST, Lin DW, Mostaghel EA *et al*.** persistent intraprostatic androgen concentrations after medical castration in healthy men. *J Clin Endocrinol Metab* 2006; **91**: 3850–6
19 **Mizokami A, Koh E, Fujita H *et al*.** The adrenal androgen androstenediol is present in prostate cancer tissue after androgen deprivation therapy and activates muatted androgen receptor. *Cancer Res* 2004; **64**: 765–71
20 **Bélanger B, Bélanger A, Labrie F *et al*.** Comparison of residual C-19 steroids in plasma and prostatic tissue of human, rat, and guinea pig after castration: unique importance of extratesticular androgens in men. *J Steroid Biochem* 1989; **32**: 695–708
21 **Nishiyama T, Hashimoto Y, Takahashi K.** The influence of androgen deprivation therapy on dihydrotestosterone levels in the prostatic tissue of patients with prostate cancer. *Clin Cancer Res* 2004; **10**: 7121–6
22 **Nishiyama T, Ikarashi T, Hashimoto Y *et al*.** The change in the dihydrotestosterone level in the prostate before and after androgen deprivation therapy in connection with prostate cancer aggressiveness using the Gleason score. *J Urol* 2007; **178**: 1282–8
23 **Mohler JI, Gregory CW, Ford OH *et al*.** The androgen axis in recurrent prostate cancer. *Clin Cancer Res* 2004; **10**: 440–8
24 **Titus MA, Schell MJ, Lih FB *et al*.** Testosterone and dihydrotestosterone tissue levels in recurrent prostate cancer. *Clin Cancer Res* 2005; **11**: 4653–7
25 **Marks LS, Mazer NA, Mostaghel E *et al*.** Effect of testosterone replacement therapy on prostate tissue in men with late-onset hypogonadism: a randomized controlled trial. *JAMA* 2006; **296**: 2351–61
26 **van der Sluis TM, Vis AN, van Moorselaar RJA *et al*.** Intraprostatic testosterone and dihydrotestosterone. Part I: methods of determination, and concentrations in men with benign prostatic hyperplasia and prostate cancer. *BJU Int* 2011 (in press)
27 **Culig Z, Hoffmann J, Erdel M *et al*.** Switch from antagonist to agonist of the androgen recepor bicalutamide is associated with prostate tumour progression in a new model system. *Br J Cancer* 1999; **81**: 242–51
28 **Gregory CW, Johnson RT, Mohler JL *et al*.** Androgen receptor stabilization in recurrent prostate cancer is associated with hypersensitivity to low androgen. *Cancer Res* 2001; **61**: 2892–8

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Abbreviations: **ADT**, androgen deprivation therapy; **5AR**, 5- -reductase; **DHT**, dihydrotestosterone; **DES**, diethylstilbestrol; **CRPC**, castration-resistant prostate cancer; **LOH**, late onset hypogonadism; **TRT**, testosterone replacement therapy.

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