

## Effects of androgen deficiency and replacement on prostate zonal volumes

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(Received 29 July 2000; returned for revision 22 August 2000; finally revised 22 October 2000; accepted 6 December 2000)

### Summary

**BACKGROUND AND OBJECTIVES** Androgens play a key role in prostate development and disease. However the effects of androgen deficiency and replacement on the prostate during mid-life are not well understood, and there is no information on their effects on prostate zonal volumes. This study aimed to define the effects of androgen deficiency and androgen replacement therapy on prostate zonal volumes (central, peripheral & total) using planimetric prostate ultrasound with particular emphasis on the central zone of the prostate, the most hormonally sensitive and fastest growing region of the prostate and the zone where nodular benign prostate hyperplasia originates.

**PATIENTS AND MEASUREMENTS** Central and total prostate volume were measured directly, and peripheral prostate volume calculated, by a single observer using transrectal ultrasound in 71 hypogonadal men (aged  $40 \pm 2$ , range 18–78 years) who were compared with individually age-matched health controls without prostate or gonadal disease. Among the men with androgen deficiency, 17 men had untreated androgen deficiency (never treated or no treatment for at least 6 months) and 54 men were receiving long-term androgen replacement therapy (median 32 months, 93%  $\geq 6$  months) with testosterone implants ( $n = 27$ ), testosterone ester injections ( $n = 24$ ) or other testosterone treatment ( $n = 3$ ).

**RESULTS** Compared with individually age-matched controls, untreated androgen deficient men ( $n = 17$ ) had reduced central ( $4.0 \pm 0.5$  vs.  $6.2 \pm 0.5$  ml,  $P < 0.001$ ) and total ( $23.4 \pm 2.6$  vs.  $29.2 \pm 1.6$  ml,

$P < 0.001$ ) prostate volumes whereas the reduction in peripheral prostate volume ( $19.4 \pm 2.1$  vs.  $23.0 \pm 1.3$  ml,  $P = 0.15$ ) was not statistically significant. Men with treated androgen deficiency ( $n = 54$ ) also still had significantly reduced central ( $4.8 \pm 0.4$  vs.  $6.8 \pm 0.4$ ,  $P < 0.001$ ), peripheral prostate volume ( $19.6 \pm 0.8$  vs.  $21.6 \pm 0.7$  ml,  $P = 0.06$ ) and total ( $24.4 \pm 1.1$  vs.  $28.4 \pm 1.0$  ml,  $P = 0.008$ ) despite prolonged restoration of physiological testosterone concentrations. Neither modality of testosterone treatment nor type of hypogonadism influenced prostate zonal volumes before or after treatment. In contrast, central, peripheral and total prostate volume increased with age among healthy controls and men with androgen deficiency regardless of androgen replacement therapy. Plasma PSA concentrations were reduced in men with untreated androgen deficiency and were similar to age-matched controls in men with treated androgen deficiency.

**CONCLUSIONS** We conclude that, during mid-life, chronic androgen deficiency due to hypogonadism is associated with reduced central, peripheral and total prostate volumes. Reduced prostate volumes persist even during long-term maintenance of effective androgen replacement therapy with physiological testosterone concentrations until the fourth decade of life. After that, prostate volumes increase with age regardless of androgen deficiency or replacement. These findings suggest that, during mid-life, age is a more important determinant of prostate growth than ambient testosterone concentrations maintained in the physiological range. The persistently subnormal prostate volumes despite adequate androgen replacement therapy may explain the apparent paucity of cases of overt prostate disease among testosterone-treated androgen deficient men who retain protection against prostate disease despite physiological androgen replacement therapy.

The prostate is the classical androgen-dependent organ in its growth and development (Cunha *et al.*, 1987). Full prostate development requires a normal androgen receptor (Quigley *et al.*, 1995) expressed in the embryonic prostatic mesenchyme (Cunha *et al.*, 1987). Maintenance of prostate development requires continued exposure to adult male blood concentrations

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of testosterone secreted from the testis (Wu & Gu, 1987) together with intraprostatic conversion of testosterone to the more potent pure androgen 5 $\alpha$ -dihydrotestosterone (Imperato-McGinley *et al.*, 1992). In later life, after decades of exposure to adult male blood testosterone concentrations, the common prostate diseases, benign prostatic hyperplasia (BPH) and prostate cancer, increase sharply with age (Berry *et al.*, 1984).

Severe, uncorrected androgen deficiency prior to puberty due to prepubertal castration (Wu & Gu, 1987) or genetic defects such as androgen receptor mutation (Quigley *et al.*, 1995) or type II 5 $\alpha$ -reductase deficiency (Imperato-McGinley *et al.*, 1992) (the latter abrogating the intraprostatic androgen amplification system) strikingly impede prostate development. The effects of androgen deficiency and replacement on the prostate during mid-life are less well understood. Previous studies have shown consistently that untreated androgen deficiency is associated with a smaller total prostate volume and lower circulating PSA concentrations (Canale *et al.*, 1990; Sasagawa *et al.*, 1990; Behre *et al.*, 1994; Meikle *et al.*, 1997; Ozata *et al.*, 1997). Few studies however, have used the accurate planimetric methodology and included age-matched health controls (Behre *et al.*, 1994; Sasagawa *et al.*, 1990); none have studied the effects of androgen deficiency and replacement on central or peripheral prostate zonal volumes.

The present study aimed to examine the effects of androgen deficiency and androgen replacement therapy on the prostate using planimetric prostate ultrasound to measure central, peripheral and total prostate volumes. Planimetric ultrasound remains the reference method for accurate measurements of prostate volumes. This study features measurement of the sonographically defined central zone of the prostate, encompassing the anatomical transitional zone, which is both the region of the prostate most sensitive to hormonal changes as well as the region where the nodular hyperplasia of BPH originates. This ultrasonically defined region of the prostate includes the anatomically defined transition zone wherein BPH originates (McNeal, 1978; McNeal, 1983). Our previous studies (Jin *et al.*, 1996; Jin *et al.*, 1999; Jin *et al.*, 1999) as well as those of others in man (Bosch *et al.*, 1994) and primates (Habenicht *et al.*, 1987; Habenicht & El-Etreby, 1988) have shown consistently that the central zone of the prostate is the most hormonally sensitive (Habenicht & El-Etreby, 1988; Habenicht *et al.*, 1987; Jin *et al.*, 1996) and the zone that grows most quickly with age (Bosch *et al.*, 1994).

## Materials and methods

### Patients

Androgen deficient men attending the Andrology Unit, Royal Prince Alfred Hospital, for androgen replacement

therapy were recruited for this study. Exclusion criteria for this study were for men with proven prostate disease or anorectal disorders, which precluded safe use of the transrectal probe. Age-matched healthy controls without known prostate or endocrine disease were obtained from a concurrent epidemiological study of the prostate in healthy men which used the same ultrasound observer, equipment and assays (Jin *et al.*, 1999). Patients received long-term androgen replacement therapy with either testosterone implants, typically four 200 mg testosterone implants (Organon) per 6 months, or regular testosterone ester intramuscular injections, typically 250 mg mixed testosterone esters (Sustanon™, Organon) per 2 weeks, or oral testosterone undecanoate (160–240 mg per day, Andriol™, Organon) as described previously (Conway *et al.*, 1988; Handelsman *et al.*, 1990). This study received ethical approval from the Central Sydney Area Health Service (RPAH Zone) Ethics Review Committee within NHMRC Guidelines for Human Experimentation.

### Prostate ultrasound

The prostate was visualized and measured by a high-resolution, B model, real-time ultrasound equipment (OPUS 1, Sydney) using a 7.5-MHz biplane and sector transrectal transducer as described previously by a single observer (Jin *et al.*, 1996; Jin *et al.*, 1999). If digital rectal examination of the prostate was normal, the rectal transducer probe (2 mm diameter) was gently inserted 3–5 cm into the rectum. The rectal probe was covered with a disposable rubber sheath coated inside with a water soluble lubricant (K-Y Jelly, Johnson and Johnson Ltd, UK) and outside with gel (AQUASONIC, Parker Laboratories, New Jersey, USA). A calibrated stepper device was used to facilitate measurement of prostate cross-sectional areas at 2.5 mm step intervals from the base to apex of the prostate. At each step, the cross-sectional area of the whole prostate and its central zone were outlined with a tracker ball and the resulting image was digitized, analysed and stored. From the sequential prostate cross-sectional areas, the central prostate volume (CPV) and total prostate volume (TPV) were calculated by the 3 dimensional equivalent of the trapezoidal rule using the sequence of cross-sectional areas at fixed step intervals. The sonographically defined central prostate volume (CPV) included the anatomical areas of the transition zone, central zone and anterior fibromuscular stroma according to the zonal description of McNeal (McNeal, 1978; McNeal, 1983). The peripheral prostate volume (PPV) was calculated as the difference between CPV and TPV. The planimetric ultrasound procedure took an average of 10 minutes (range 5–15 minutes). All results were recorded on a video processor (P67E, MITSUBISHI). Reproducibility of total prostate volume measurements, estimated as a coefficient of variability from 13 healthy

men without known prostate disease who underwent two ultrasound studies at a median of 3 months (range 0.5–11 months) apart was 8.4% for central, 7.3% for peripheral and 13.8% for total prostate volume.

### Assay

Blood samples were taken before rectal examination or probe insertion for measurement of total and free testosterone, LH, FSH, SHBG, prostate-specific antigen and prostatic acid phosphatase by commercial immunoassays (Handelsman *et al.*, 1995; Handelsman *et al.*, 1996; Jin *et al.*, 1999; Jin *et al.*, 1999).

### Data analysis

Data were expressed as mean and standard error of the mean. Age-matched groups were compared by *t*-test and ANOVA as required with all analyses verified by appropriate nonparametric tests to exclude the effects of nongaussian distribution on analysis. Two-tailed *P*-values < 0.05 were considered statistically significant.

## Results

### Patients and controls

Overall, 71 hypogonadal patients (aged 18–78 years) were studied together with 71 individually age-matched controls selected from a concurrent epidemiological cohort study of

age-specific prostate zonal volumes in healthy Australian men. Hypogonadism was primary (hypergonadotrophic) in 48 (68%) with underlying causes being Klinefelter's syndrome (12), castration (16) and testicular damage (20). The remaining 23 (32%) had secondary (hypogonadotrophic) hypogonadism due to idiopathic hypogonadotrophic hypogonadism or Kallmann's syndrome (12), pituitary or hypothalamic tumours (eight), haemochromatosis (two) and mixed aetiology (one). Among 54 patients receiving long-term androgen replacement therapy (median 32 months, range 1–145 months; 45/54 (83%) for  $\geq 12$  months and 50/54 (93%) for  $\geq 6$  months) at the time of study, 27 were having regular testosterone implants (typically four 200 mg testosterone implants (Organon) per 6 months) and 24 regular testosterone ester intramuscular injections (typically 250 mg mixed testosterone esters (Sustanon™, Organon) per 2 weeks) with the remainder ( $n = 3$ ) receiving other therapy as described previously (Conway *et al.*, 1988; Handelsman *et al.*, 1990). Mean testicular volume (by orchidometry) was smaller in hypogonadal patients compared with healthy controls ( $7 \pm 1$  ml *vs.*  $22 \pm 1$  ml).

### Prostate zonal volumes

Central prostate volume was reduced in all androgen deficient men ( $n = 71$ ,  $4.6 \pm 0.3$  *vs.*  $6.7 \pm 0.3$  ml,  $P < 0.001$ ) whether or not they were treated with testosterone (Table 1) compared with their own individually age-matched controls. There was no significant effect of type of hypogonadism

**Table 1** Findings in untreated and treated men with androgen deficiency and age-matched eugonadal controls

	Untreated ( $n = 17$ )		Treated ( $n = 54$ )	
	Androgen deficient	Control	Androgen deficient	Control
Age (years)	$40 \pm 4$	$41 \pm 3$	$39 \pm 2$	$41 \pm 2$
Mean testis volume (ml)	$6 \pm 1$ *	$23 \pm 1$	$7 \pm 1$ *	$22 \pm 1$
Central PV (ml)	$4.0 \pm 0.5$ *	$6.2 \pm 0.5$	$4.8 \pm 0.4$ *	$6.8 \pm 0.4$
Peripheral PV (ml)	$19.4 \pm 2.1$	$23.0 \pm 1.3$	$19.6 \pm 0.8$	$21.6 \pm 0.7$
Total PV (ml)	$23.4 \pm 2.6$ *	$29.2 \pm 1.6$	$24.4 \pm 1.1$ *	$28.4 \pm 1.0$
Central/Peripheral ratio	$0.21 \pm 0.09$	$0.28 \pm 0.02$	$0.24 \pm 0.10$	$0.32 \pm 0.02$
Central/Total ratio	$0.17 \pm 0.01$ *	$0.21 \pm 0.01$	$0.19 \pm 0.01$ *	$0.23 \pm 0.01$
Total testosterone (nmol/l)	$6.5 \pm 1.1$ *	$16.8 \pm 1.6$	$17.2 \pm 1.9$ †	$15.9 \pm 0.8$
Free testosterone (pmol/l)	$85 \pm 18$ *	$242 \pm 21$	$271 \pm 34$ †	$249 \pm 14$
§LH (U/l)	$13.9 \pm 1.9$ *	$4.9 \pm 0.9$	$10.4 \pm 2.3$ * †	$4.7 \pm 0.5$
§FSH (U/l)	$31.1 \pm 5.0$ *	$6.0 \pm 1.4$	$22.1 \pm 4.7$ * †	$6.1 \pm 0.7$
SHBG (nmol/l)	$31.2 \pm 4.3$	$40.0 \pm 5.5$	$33.6 \pm 2.0$ *	$42.4 \pm 2.1$
PSA ( $\mu$ g/l)	$0.6 \pm 0.1$ *	$0.9 \pm 0.1$	$1.0 \pm 0.2$	$1.1 \pm 0.2$
PSA density ‡	$0.023 \pm 0.005$ *	$0.031 \pm 0.003$	$0.038 \pm 0.005$	$0.041 \pm 0.007$
Prostatic acid phosphatase ( $\mu$ g/l)	$1.3 \pm 0.1$	$1.3 \pm 0.1$	$1.4 \pm 0.1$	$1.1 \pm 0.1$

\* $P < 0.05$  *vs.* their own 1 : 1 age-matched controls; † $P < 0.05$  *vs.* untreated men; ‡defined as plasma PSA concentration (in  $\mu$ g/l) divided by total prostate volume (in ml); §restricted to men with untreated ( $n = 13$ ) and treated ( $n = 35$ ) primary hypergonadotrophic hypogonadism and their own age-matched controls ( $n = 48$ ).

(primary  $4.6 \pm 0.4$  vs. secondary  $4.6 \pm 0.5$  ml,  $P = 0.70$ ) or modality of treatment (implants  $5.1 \pm 0.5$  vs. injections  $4.4 \pm 0.5$  ml,  $P = 0.56$ ) on central prostate volumes.

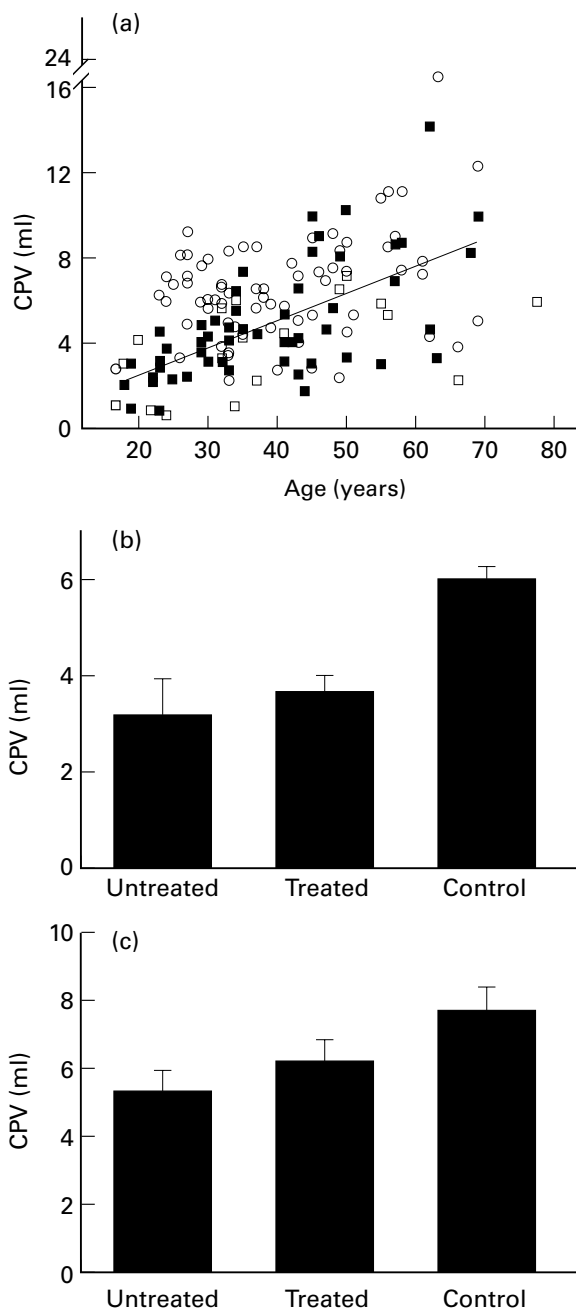
Peripheral prostate volume was significantly reduced in all androgen deficient men ( $n = 71$ ,  $19.6 \pm 0.8$  vs.  $21.9 \pm 0.6$  ml,  $P = 0.02$ ). The reduction in peripheral prostate volume was marginally significant among those treated with testosterone (Table 1,  $P = 0.06$ ) but not significant among the untreated ( $P = 0.15$ ) compared with individually age-matched controls. There was no significant effect of type of hypogonadism (primary  $19.7 \pm 1.0$  vs. secondary  $19.4 \pm 1.4$  ml,  $P = 0.66$ ) or modality of treatment (implants  $21.2 \pm 0.9$  vs. injections  $17.6 \pm 1.3$  ml,  $P = 0.11$ ) on peripheral prostate volumes.

Total prostate volume was reduced in all androgen deficient men ( $n = 71$ ,  $24.2 \pm 1.0$  vs.  $28.6 \pm 0.8$  ml,  $P < 0.001$ ) whether treated with testosterone or not (Table 1) compared with individually age-matched controls. There was no significant effect of type of hypogonadism (primary  $24.3 \pm 1.3$  vs. secondary  $24.0 \pm 1.6$  ml,  $P = 0.67$ ) or modality of treatment (implants  $26.3 \pm 1.2$  vs. injections  $22.1 \pm 1.7$  ml,  $P = 0.23$ ) on total prostate volumes.

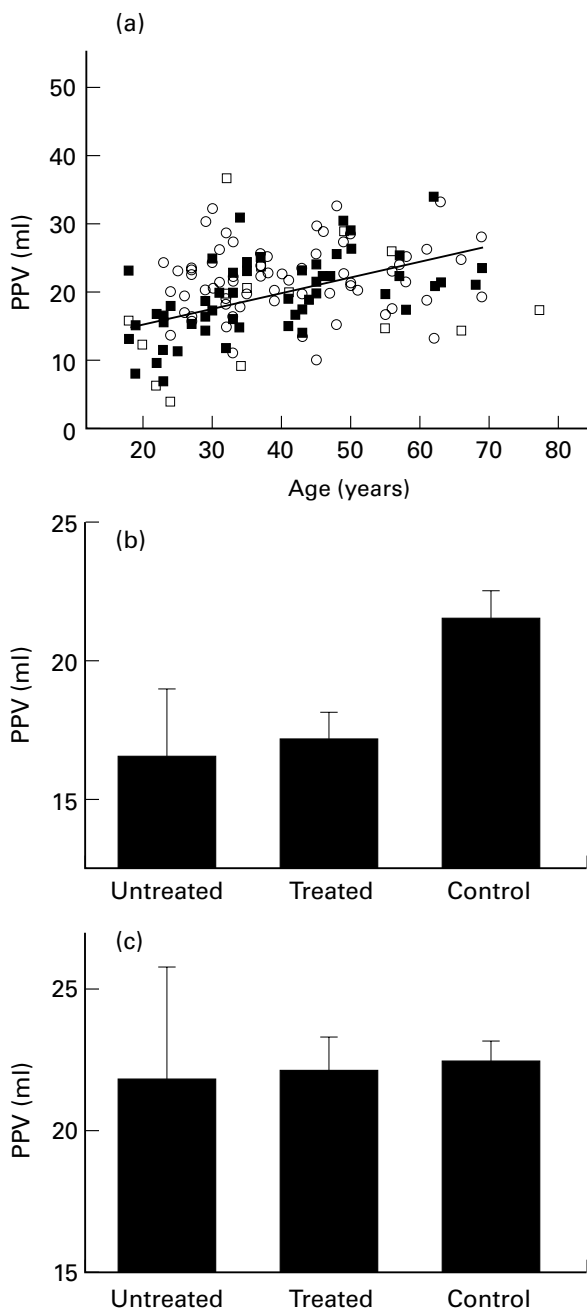
Central (Fig. 1), peripheral (Fig. 2) and total (Fig. 3) prostate volumes were strongly correlated with age ( $r = 0.642$ ,  $0.322$  &  $0.642$ , respectively). When grouped according to age ( $< 40$  years vs.  $> 40$  years), among men under the age of 40 years, central, peripheral and total prostate volumes remained lower among androgen deficient men, whether treated or not, compared with age-matched controls; in men over the age of 40 years, only central prostate volume remained marginally lower ( $P = 0.06$ ) whereas peripheral and total prostate volumes were similar in androgen deficient (treated or not) and age-matched control men. Duration of testosterone treatment in the treated androgen deficient men did not correlate significantly with central ( $r = 0.182$ ,  $P = 0.090$ ), peripheral ( $r = 0.075$ ,  $P = 0.292$ ) or total ( $r = 0.008$ ,  $P = 0.477$ ) prostate volumes.

#### Biochemical tests

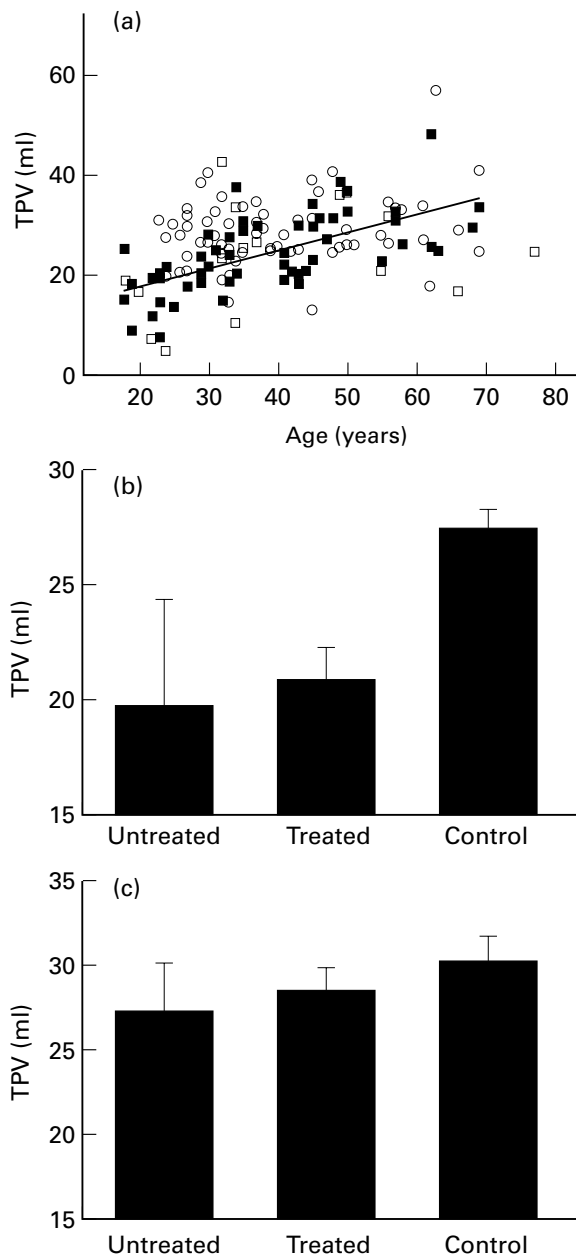
PSA concentrations were significantly lower among men with untreated androgen deficiency ( $n = 17$ ,  $0.6 \pm 0.1$  vs.  $0.9 \pm 0.1$  ng/ml,  $P = 0.04$ ) compared with healthy age-matched controls (Table 1). PSA concentrations in men with treated androgen deficiency ( $n = 54$ ,  $1.0 \pm 0.2$  ng/ml) was marginally higher than untreated androgen deficiency ( $n = 17$ ,  $0.6 \pm 0.1$  ng/ml,  $P = 0.078$ ) but similar to healthy age-matched controls ( $n = 54$ ,  $1.1 \pm 0.2$  ng/ml,  $P = 0.35$ ). PSA concentrations were positively correlated with central, total and peripheral prostate volumes in androgen deficient



**Fig. 1** (a) Plot of central prostate volume (CPV; ml) against age (years) for men with untreated ( $\square$ ) and treated ( $\blacksquare$ ) androgen deficiency and age-matched healthy controls ( $\circ$ ). Linear regression for all data indicated by solid line ( $r = 0.64$ ,  $P < 0.001$ ). The same data for the three groups of men in are displayed in histograms categorized by age into men (b) under and (c) over the age of 40 years.



**Fig. 2** (a) Plot of peripheral prostate volume (PPV; ml) against age (years) for men with untreated (□) and treated (■) androgen deficiency and age-matched healthy controls (○). Linear regression for all data indicated by solid line ( $r = 0.56$ ,  $P < 0.001$ ). The same data for the three groups of men in are displayed in histograms categorized by age into men (b) under and (c) over the age of 40 years.



**Fig. 3** (a) Plot of total prostate volume (TPV; ml) against age (years) for men with untreated (□) and treated (■) androgen deficiency and age-matched healthy controls (○). Linear regression for all data indicated by solid line ( $r = 0.64$ ,  $P < 0.001$ ). The same data for the three groups of men in are displayed in histograms categorized by age into men (b) under and (c) over the age of 40 years.

( $r = 0.62, 0.49, 0.39$ , respectively, all  $P < 0.001$ ) but not control ( $r = 0.09, -0.01, 0.07$ , all  $P > 0.2$ ) men.

Prostatic acid phosphatase was unaffected by androgen deficiency or replacement therapy (Table 1).

Plasma total and free testosterone concentration were significantly reduced in untreated androgen deficient men but treatment of androgen deficiency significantly increased plasma testosterone concentrations to levels that were indistinguishable from healthy age-matched controls (Table 1). Neither total nor free testosterone were correlated with central, total or peripheral prostate volumes (all  $r < 0.12$ ,  $P > 0.15$ ).

In men with primary (hypergonadotrophic) hypogonadism, LH and FSH level were higher in untreated androgen deficient men and androgen replacement therapy significantly reduced plasma gonadotrophin levels but both LH and FSH remained significantly higher than in healthy age-matched controls (Table 1).

SHBG concentration was lower in androgen deficient men regardless of treatment compared with healthy age-matched controls (Table 1). SHBG concentrations were not correlated with any prostate zonal volumes.

## Discussion

The prostate is the classical androgen dependent organ. Full development is completed only after puberty in the presence of adult male blood testosterone concentrations together with a normally functional androgen receptor (Quigley *et al.*, 1995) and type II 5 $\alpha$ -reductase (Imperato-McGinley *et al.*, 1992). As adrenal androgens cannot support prostate growth (Oesterling *et al.*, 1986), it is testicular androgens, notably testosterone, that are the major hormonal influence on prostate growth in mid-life. Maintenance of prostate growth however, requires not only testosterone but also an intraprostatic androgen amplification system, the type II 5 $\alpha$ -reductase, which converts most incoming testosterone to the more potent androgen, 5 $\alpha$ -dihydrotestosterone. Decades after full prostate development and with continuing exposure to adult male blood testosterone concentrations, the human prostate remains androgen sensitive and frequently develops benign and malignant diseases while circulating androgen levels are gradually falling. Strikingly, however, the seminal vesicles, with similar developmental origin and androgen sensitivity, virtually never develop significant disease throughout life. Hence the precise relationship between androgens and the origins of prostate disease remain unclear.

The present study confirms previous observations that men with untreated androgen deficiency have reduced total prostate volume when measured by simple 3-dimensional ellipsoidal calculation (Canale *et al.*, 1990; Meikle *et al.*, 1997; Ozata *et al.*, 1997) or by the more accurate planimetric reconstruction (Sasagawa *et al.*, 1990; Behre *et al.*, 1994) of prostate volume. The present study, using refined planimetric methodology, extends those findings to show that central and peripheral zonal volumes are both reduced in androgen deficiency.

Similarly, the present study confirms the reduction in PSA concentrations in untreated androgen deficiency and its increase during androgen replacement therapy (Behre *et al.*, 1994; Meikle *et al.*, 1997; Ozata *et al.*, 1997) to levels comparable with healthy eugonadal men of the same age (Behre *et al.*, 1994). This is consistent with the general relationship between PSA and total prostatic epithelial mass. Interestingly the PSA concentration was more sensitive to testosterone treatment than was total prostate volume, suggesting that the efficiency of prostate epithelial cell synthesis and secretion of PSA per cell is positively influenced by testosterone more than is cellular proliferation. This is also consistent with the findings that PSA secretion is more rapidly changed by endogenous (Vieira *et al.*, 1994) or exogenous (Ozata *et al.*, 1997) androgens than is the relatively slow growth of the prostate. The reduction in prostate volumes in the men with untreated androgen deficiency was greatest for central (35%) than for peripheral (16%) and total (20%) prostate volume. This again highlights the greater hormonal sensitivity of the central zone of the prostate in the human (Jin *et al.*, 1996; Jin *et al.*, 1999; Jin *et al.*, 1999) where benign prostatic hyperplasia originates (McNeal, 1978; McNeal, 1983) as well as in the nonhuman primate (Habenicht *et al.*, 1987; Habenicht & El-Etreby, 1988).

A novel and unexpected finding in this study is that prostate zonal volumes remain diminished in men receiving long-term androgen replacement therapy. This result conflicts previous studies reporting that androgen replacement therapy restores total prostate volume to levels comparable with healthy age-matched controls (Behre *et al.*, 1994; Sasagawa *et al.*, 1990) although there are no previous data on prostate zonal volumes. It is difficult to reconcile the discrepancy between these three studies of total prostate volume, each of which used planimetry and had similar aged study populations. Possible reasons for the discrepancy include the tighter (individual *vs.* groupwise) matching of controls or more refined planimetric measurement technique (2.5 mm *vs.* 5 mm steps) in the present study. Another possibility is that, because about half were having testosterone implants and the prostate studies mostly coincided with the next testosterone dose, prostate volumes may have been underestimated due to lower ambient blood testosterone concentrations. This contention is supported by the LH levels which remained incompletely suppressed at the time of study among men with primary (hypergonadotrophic) hypogonadism when suppression into the eugonadal range is expected with adequate androgen replacement. There are several reasons why this explanation may not correct. First, the findings were equally evident among the other half of the men who were receiving testosterone ester injections for androgen replacement therapy. Second, this possibility does not account for or negate the uneven influence of age. Third, prostate volume

shrinkage is sluggish even following complete androgen withdrawal (Kamischke *et al.*, 1997) and men undergoing regular androgen replacement therapy do not tolerate severe or prolonged androgen deficiency symptoms. It remains impossible to exclude other unidentified differences in the patient populations or treatment regimens.

The lack of relationship between ambient blood testosterone concentration and prostate volume is similar to the finding that anabolic steroid abusers demonstrate no increase in total prostate volume or PSA (although central prostate volume was increased) despite massive androgen doses (Jin *et al.*, 1996). Nor does exogenous testosterone at more physiological doses increase PSA concentrations in eugonadal men (Cooper *et al.*, 1998). On the other hand, the effects of age on prostate growth were considerably greater than any apparent relationship to androgens particularly after mid-life. These findings are consistent with those of a twin study which identified similar differences in patterns of prostate zonal growth before and after the age of 50 years including that blood androgens related inversely, or not at all, to prostate zonal volumes (Meikle *et al.*, 1997).

An alternative interpretation for the lack of relationship between ambient testosterone concentrations and prostatic volumes is that intraprostatic factors may be important. For example, most testosterone entering the prostate is reduced by 5 $\alpha$  reductase type II to the more potent, nonaromatisable androgen, dihydrotestosterone. The present findings are consistent with the concept that the intraprostatic potency amplification mechanism for androgens that can be activated by 5 $\alpha$  reduction (including testosterone but excluding dihydrotestosterone or 7 $\alpha$ -methyl 19-nortestosterone (Sundaram *et al.*, 1995)) dictates the relationship between ambient plasma testosterone concentration and prostatic volumes. The present findings and uncertainties reinforce the need for more sophisticated appreciation of the relationship of ambient testosterone concentrations with prostate growth and pathology.

An important consideration for interpretation of the persistent reduction in prostate zonal volumes is whether the androgen-deficient men were receiving adequate androgen replacement. The adequacy of androgen replacement therapy is supported by the use of standard androgen dosage (Conway *et al.*, 1988; Handelsman, 1998) in long-term patients familiar with their own androgen deficiency symptoms. Their high continuation rates in treatment (Handelsman *et al.*, 1997) confirms their satisfaction with treatment. Furthermore, plasma total and free testosterone concentrations were normalized by androgen replacement therapy to levels comparable with eugonadal controls and analysis of bone density indicates normalization to eugonadal controls during similar treatment (Handelsman, unpublished). On the other hand, among the androgen deficient men with hypergonadotrophic hypogonadism,

LH concentrations were reduced but not normalized. As LH concentrations can be expected to be normalized in men with hypergonadotrophic hypogonadism receiving adequate androgen replacement therapy (Conway *et al.*, 1988; Handelsman *et al.*, 1990; Handelsman, 1998), this might suggest suboptimal androgen replacement therapy. About half the men recruited for this study were being treated regularly with testosterone implants which last approximately 6 months, a lower proportion than our clinic overall. This is because newly referred men, most dissatisfied, or having problems with testosterone ester injections, usually prefer to switch to testosterone implant therapy when offered the choice (Conway *et al.*, 1988). The study participants generally underwent prostate ultrasound study at the time they returned for next testosterone implant at which time the previous treatment had run out. Hence, this unintended bias in their involvement in the study may explain the discrepancy between men generally having adequate androgen replacement therapy and yet having incomplete LH suppression at the time of study. How much the timing of the prostate ultrasound study in relation to hormone treatment influenced the findings is unclear.

The persistent reduction in prostate volumes may explain the impression that men with androgen deficiency have persistent protection from prostate disease compared with eugonadal men of similar age. This is particularly notable since regular surveillance of men with one condition (hypogonadism requiring androgen replacement) is well known to artefactually increase ('detection bias' (Sackett, 1979)) the likelihood of identifying additional disorders. Despite this detection bias, prostate disease is rarely reported among men with genuine androgen deficiency due to pituitary or testicular disorders. Although often stated in textbooks that castration early in life prevents prostate disease in later life, this plausible statement has limited empirical foundation. This maxim appears to originate from the work of Moore (Moore, 1944) who, in reviewing his experience and the pathology literature, identified 28 'eunuchs' among whom no evidence of prostatic hyperplasia was reported compared with his expectation of a prevalence of ~50% at that age. He further commented that no cases of prostate cancer had been reported among 'eunuchs or eunuchoids' (Moore, 1944). Nevertheless there were prior reports of BPH among men with long-standing androgen deficiency (Deming *et al.*, 1935; Kretschmer, 1935; Deming & Neumann, 1939) subsequently confirmed by examples of BPH (Cox *et al.*, 1989; Scott, 1953; Yokoyama *et al.*, 1989) and prostate cancer (Sharkey & Fisher, 1960; Boccon-Gibod *et al.*, 1991; Pienkos & Meissner, 1991; Uno *et al.*, 1998) among men with long-standing severe androgen deficiency. Nevertheless, such cases seem exceptional and the prevalence of prostate disease among men with androgen deficiency appears to be low. In the two studies with greater scope than single case

reports (Jackson *et al.*, 1989; Morgenthaler *et al.*, 1996), both identified only noninvasive prostate cancer by biopsies among ageing men with lowered testosterone levels. With the exception of a single case in the smaller study (Jackson *et al.*, 1989), none of these men had pituitary or testicular disorders causing genuine longstanding androgen deficiency. Hence apart from exceptional individual cases, invasive prostate cancer appears to be rare among men with androgen deficiency even during androgen replacement therapy. Further large case series with a well defined diagnostic and population bases would help to verify this observation and relatively large case-control studies of older men presenting with invasive prostate cancer would be required to estimate the magnitude of the protective effect.

The biological basis of such a protective effect of androgen deficiency persisting even during androgen replacement therapy may relate to the operations of the intraprostatic androgen amplification mechanisms or to the different spectrum of circulating endogenous androgens and oestrogens produced by the testis compared with that produced by administration of testosterone for androgen replacement therapy. These findings may also suggest that the prevention or retardation of benign prostate disease may be considered among the noncontraceptive benefits of hormonal male contraception.

An important finding from this study is that age had consistently strong effects on prostate zonal volumes in both androgen deficient and control men. If the hormonal sensitivity of the central zone of the prostate is any indicator of susceptibility to later development of nodular prostatic hyperplasia in that region, these findings suggest that the effects of age overcome any effects of prevailing blood-borne androgen exposure. Whether this inference also extends to risk of prostate cancer which originates in different regions of the prostate remains less clear. Further analytical studies of the relationship between ambient and blood-borne androgens in mid-life and the origins of late-life prostate diseases are needed.

### Acknowledgements

The authors thank Leo Turner, Di Quinn, Susan Wishart of the Department of Andrology, Concord Hospital (and formerly the Andrology Unit, Royal Prince Alfred Hospital) for their invaluable contributions which made this study possible.

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