0021-972X/05/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 90(11):6055–6063

doi: 10.1210/jc.2005-1214

Growth and Development during Early Manhood as Determinants of Prostate Size in Later Life

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Background: Age and androgens are key determinants of benign prostate hyperplasia, but the mechanisms remain unclear. We examine the relationship between androgens and total, central, and peripheral prostate volume with a focus on early life factors.

Methods: We conducted a cross-sectional observational study of 406 community-dwelling Australian men aged 20–82 yr old without known prostate disease. Prostate zonal (total, central, and peripheral) volumes were measured by planimetric transrectal ultrasound. Participants completed questionnaires, underwent physical examination, and provided blood samples to measure total, free, and bioavailable testosterone, dihydrotestosterone, estradiol, SHBG, LH, FSH, and prostate-specific antigen.

Results: Prostate zonal volumes were positively associated with age, prostate-specific antigen, early onset of puberty, current height, body surface area, lean body mass, hip and waist circumference as well as recalled height and weight during puberty and adolescence but not current weight, fat mass, or body mass index. Stepwise multivariate regression modeling indicated that age and height were the only independent predictors of prostate zonal volumes. When adjusted for age and sampling time of day, the negative correlations of age-adjusted prostate zonal volumes with current blood total, free, and bioavailable testosterone and the positive correlation with blood SHBG were no longer significant.

Conclusions: This study suggests that early and long-term androgen exposure may have long-acting effects on mature prostate zonal volumes, whereas relationships with current blood androgens and related hormones levels were mostly a result of confounding by age. Additional studies on the mechanism of androgen effects on late-life prostate diseases should consider lasting effects of early-life androgen exposure. **(*J Clin Endocrinol Metab* 90: 6055–6063, 2005)**

BENIGN PROSTATIC HYPERPLASIA (BPH) is a frequent condition among older men (1). Men have over 80% lifetime likelihood of developing this nodular benign tumor originating within the central or transitional zone of the prostate (2). Most will suffer symptoms, and half of symptomatic men may require prostatectomy (3). BPH is therefore among the most common medical conditions and its surgical treatment among the greatest medical costs in the community. Although the natural history of BPH is known from autopsy data using total prostate weight as a surrogate variable (1), its determinants remain poorly understood (4). Although age and androgen exposure during manhood are clearly established determinants, most other factors identified by clinical or epidemiological research remain inconsistent between studies (5). Much of this inconsistency is attributable to the variable definitions of BPH used in studies (6). Clinical criteria for BPH diagnosis vary from surgical, in patients undergoing prostatectomy, to clinical according to presence of lower urinary tract symptoms (LUTS) and/or prostate enlargement detected by digital rectal examination. Yet these definitions are neither specific nor always concordant. For example, access to medical care, including affordable surgery as well as other biological influences on LUTS such as autonomic and bladder dysfunction (7), all introduce confounding and misclassifications that may nullify genuine or generate artifactual relationships.

Although timely androgen exposure is critical to prostate development, growth, and disease (8), the precise mechanism and pathophysiological consequences of androgen action on the prostate remain unclear. Exposure to high blood testosterone levels is critical for prostate development during intrauterine life (8), to maintenance of normal prostate size during adult life (9, 10), and after decades of exposure, for the development of late-life prostate diseases including BPH. Yet the precise timing of androgen effects crucial for the development of BPH is largely unknown. In trying to better establish the natural history and mid-life determinants of late-life prostate growth, prospective studies of blood testosterone levels are impractically long and retrospective case-control studies are mostly limited to blood testosterone measurements at a single time point at the time of study. An alternative is to use surrogate variables for testosterone action during different periods of life as a way of evaluating past androgen action.

This study aimed to evaluate early and long-term effects of androgens on late-life prostate volume using surrogate variables reflecting pubertal and adolescent growth and development, a process that is strongly androgen dependent. This study also featured an accurate, objective measure of prostate size, ultrasonic measurement of prostate zonal volumes, as the main endpoint. Because BPH originates in the central zone (2) with nodular growth causing progressive

First Published Online August 30, 2005

Abbreviations: BMI, Body mass index; BPH, benign prostatic hyperplasia; BSA, body surface area; BT, bioavailable testosterone; CV, coefficient of variation; DHT, dihydrotestosterone; FT, free testosterone; LUTS, lower urinary tract symptoms; PSA, prostate-specific antigen; TT, total testosterone.

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.

prostate enlargement (1), accurate measurement of total and especially central prostate zonal volume provides valuable information on BPH progression. By recruiting study participants from healthy men living in the community without known prostate disease rather than from among patients with prostate disease, this study captured a wide spectrum of stages of development of BPH and of prostate size while avoiding referral and recall bias.

Subjects and Methods

Procedures

The study population was a cross-sectional study of healthy community-dwelling men aged over 20 yr old residing in metropolitan Sydney. The study extended data obtained in a previous prostate ultrasound study (11) to include additional data collection from standardized physical examination and questionnaires. Recruitment occurred during 1998–1999 via publicity in electronic and print media. Volunteers with any history or symptoms of prostate disease (including an elevated blood PSA or abnormal digital rectal examination) requiring medical or surgical intervention or a history of endocrine disorders were excluded. The Human Ethics Review Committee of Central Sydney Area Heath Service (RPAH zone) approved the study, and participants provided written informed consent.

Each participant underwent a standard physical examination, provided a blood sample, and completed self-administered questionnaires covering socio-demographic and medical history, food frequency (12), LUTS using the International Prostate Symptom Score scale (13), and sexual function (14). The standard physical examination include measurement of height (to nearest 0.5 cm by stadiometer), weight (to nearest 0.1 kg) and hip and waist circumferences using a nonstretch tape measure as well as bioimpedance analysis (SEAC model BIM 3.0; Inderlec, Australia) after a 2-h fast to measure lean and fat body mass (in kg).

Planimetric prostate ultrasound

All participants underwent planimetric transrectal prostate ultrasound (10, 11, 15, 16) by a single observer (T.N.Z.). Briefly, the total and central prostate volumes were calculated by trapezoidal rule reconstruction using the sum of the planimetric sections measured at each step and multiplying by the stepping interval of 2.5 mm. The peripheral volume was obtained by subtracting the central volume from the total volume. The coefficient of variation was 8.3% for total and 13.8% for central zones for a single observer making repeated measurement on the same man (11). The planimetric method is objective, accurate and reproducible (17–19) and has been used in many studies for accurate volume estimation (20, 21).

Assays

Hormone assays were performed as described previously (11, 15, 22–24). Briefly, total testosterone (TT) and SHBG levels were determined by commercial immunoassays (IMMULITE* 2000; Diagnostic Products Corp., Los Angeles, CA). Interassay coefficients of variation (CV) and sensitivity for TT were less than 13% and 0.3 nmol/liter, and for SHBG they were less than 6% and 0.2 nmol/liter. Free testosterone (FT) was measured by the centrifugal ultrafiltration assay (using Centrifree micropartition system; Amicon, Beverly, MA) which gave a percent FT from which the actual blood FT concentration was calculated as the product of the blood TT concentration and the percent FT (24). The interassay CV for FT was less than 16%. Similarly, bioavailable testosterone (BT) was measured by ammonium sulfate precipitation with an intraassay CV of less than 5%. Dihydrotestosterone (DHT) was measured by the permanganate method using a T antibody (C0457; Bioquest, North Ryde, Australia). The intraassay CV for DHT was less than 5%. Blood PSA (Wallac Delfia, Turku, Finland) and other biochemical analytes were measured by routine autoanalyzer methods.

Data analysis

Total, central, and peripheral volumes were log transformed before analysis to normalize their distribution. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2) as a measure of adiposity with body surface area (BSA) calculated by the Gehan-George formula (25) as a measure of overall body size (26). Time of day for blood samples was recorded and entered into data analysis according to the 24-h clock. Statistically significant relationships were expressed in terms of exact P values and point and interval (95% confidence limits) estimates as well as effect size per unit of predictor variables, adjusted for confounding covariates where relevant. Stepwise regression used a strategy of setting $P = 0.05$ criteria for entry and removal of variables and used forward and backward stepping approaches to obtain convergent sets of variables for the final regression models. Data are expressed as mean and SE of mean unless otherwise indicated and were analyzed by NCSS software.

Results

Study population

A total of 406 men were screened for this study. After excluding six men for newly recognized medical disorders including four with histological prostate cancer, the analyses are based on data from 400 men (Table 1). Most (90%) were between the ages of 30 and 70 yr, were Caucasian (96%), spoke English at home (87%), were married (62%), and had tertiary education (65%) and university degrees (35%). Compared with the overall Sydney population according to the 2001 Census, the study volunteers had higher educational status (76, 79, 67, 58, 20, and 4%, respectively).

Age

Age was strongly correlated with central ($r = 0.575$; $P < 0.001$), total ($r = 0.512$; $P < 0.001$), and peripheral ($r = 0.418$; $P < 0.001$) volumes, which increased by 24, 14, and 10% every decade, respectively. All subsequent analyses of prostate volume were adjusted for age. Age was correlated with waist ($r = 0.364$; $P < 0.001$) and hip ($r = 0.115$; $P = 0.021$) circumference, lean ($r = -0.254$; $P = 0 < 0.001$) and fat ($r = 0.249$; $P < 0.001$) mass, height ($r = -0.254$; $P < 0.001$), and BMI ($r = 0.152$; $P = 0.002$), whereas neither weight ($r = 0.020$; $P = 0.690$) nor BSA ($r = -0.026$; $P = 0.610$) varied with age. Introduction of a quadratic curvature term (age^2) did not significantly improve the goodness of fit of regressions and was therefore not used in subsequent analyses.

PSA

Blood PSA was positively correlated with central ($r = 0.503$; $P < 0.001$), total ($r = 0.464$; $P < 0.001$), and peripheral ($r = 0.372$; $P < 0.001$) prostate zone volumes, and these correlations remained significant (all $P < 0.001$) after age adjustment ($r = 0.342$, 0.311, and 0.232, respectively) (Fig. 1).

Onset of puberty

The onset of puberty, defined as the age when pubic hair developed, was at a mean age of 13.2 ± 0.1 yr, and this correlated negatively with age-adjusted total ($r = -0.130$; $P = 0.014$), central ($r = -0.102$; $P = 0.05$), and peripheral ($r = -0.141$; $P = 0.008$) prostate volumes (Fig. 2). For each year of delay in onset of puberty, prostate volumes decreased by 2.3, 2.6, and 2.2%, respectively. Age-adjusted prostate volumes were not significantly related to other measures of adolescent development (age at voice change, shaving onset, or first ejaculation).

TABLE 1. Characteristics of participants in the study

Variables	n	Mean (SEM)	Median (Q1, Q3)	Range
Age (yr)	400	52.0 (0.6)	51 (43, 61)	20–82
Prostate sizes (ml)				
Total	399	33.5 (0.7)	30 (25, 38)	13.5–101
Central	399	10.5 (0.4)	8.4 (6.5, 12.0)	2.6–52.6
Peripheral	399	22.9 (0.4)	21.6 (18, 26)	10.3–63.0
Onset of puberty[a] (yr)	359	13.2 (0.1)	13 (12, 14)	7–20
Body weight (kg)				
14 yr old	221	57.1 (0.7)	57 (50, 64)	25–91
25 yr old	323	71.2 (0.6)	79 (64, 76)	40–120
40 yr old	287	76.8 (0.7)	76 (70, 83)	40–130
50 yr old	196	79.3 (0.8)	80 (71, 86)	45–120
Current	400	81.5 (0.6)	80.6 (72.8, 89.7)	53–142
Current body height (cm)	400	174.6 (0.3)	174.4 (171, 179)	154–197
Current BMI (kg/m^2)	400	26.7 (0.2)	26.5 (23.9, 28.9)	17.7–42.8
Current BSA (m^2)	400	2.00 (0.01)	1.98 (1.88, 2.11)	1.53–2.72
Lean body mass (kg)	377	61.4 (0.4)	61 (56, 66)	27–95
Fat body mass (kg)	377	20.1 (0.4)	19.5 (14–26)	2.4–48
Waist circumference (cm)	400	94.5 (0.5)	94 (87, 102)	66.6–131
Hip circumference (cm)	400	100.2 (0.3)	100 (96, 104)	85.3–137
TT testosterone (nmol/liter)	398	16.0 (0.3)	15.4 (12.3, 18.7)	5–39.3
FT (pmol/liter)	394	227 (4)	216 (168, 277)	60–570
BT (nmol/liter)	394	3.8 (0.1)	3.4 (2.6, 4.7)	0.9–10.3
DHT (nmol/liter)	345	2.1 (0.06)	1.8 (1.3, 2.5)	0.2–7.8
Estradiol (pmol/liter)	302	79 (1)	75 (64, 93)	22–156
SHBG (nmol/liter)	398	35.0 (0.7)	32.3 (25.7, 42.2)	10.8–113
LH (IU/liter)	399	4.6 (0.2)	4.1 (3.1, 5.4)	0.1–71
FSH (IU/liter)	399	6.1 (0.3)	5 (3.6, 6.8)	0.8–78
PSA (ng/ml)	391	1.20 (0.07)	0.8 (0.5, 1.3)	0.2–17.5
International Prostate Symptom Score	397	6.7 (0.3)	5 (2, 9)	0–31

[a] Defined as onset of pubic hair.

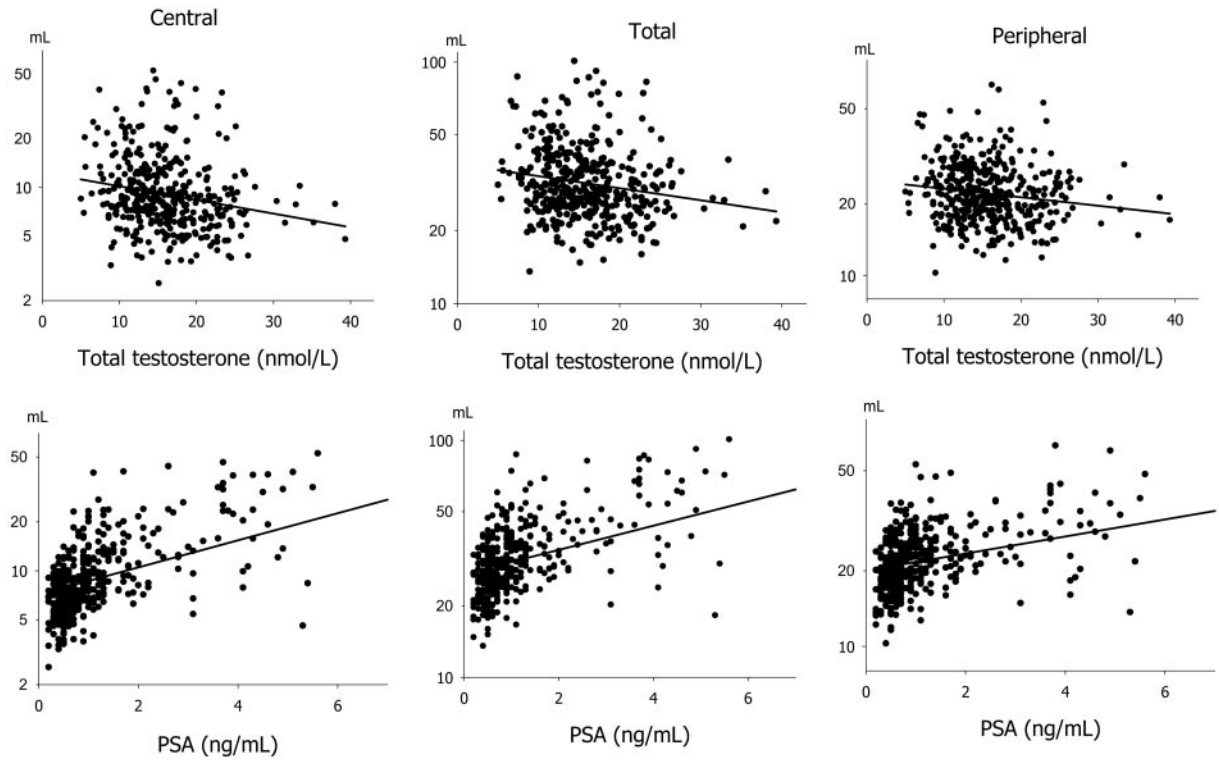

FIG. 1. Plots of central (*left*), total (*middle*), and peripheral (*right*) prostate zonal volume against TT (*top*) and PSA (*bottom*). Note logarithmic scale on the y-axis. Significant correlations are indicated by the addition of a linear regression line. Similar significant linear correlations were observed for FT and BT as for TT, but DHT, SHBG, and estradiol were not significantly correlated with prostate zonal volumes. See text for more details.

FIG. 2. Plots of central (*top*), total (*middle*), and peripheral (*bottom*) prostate zonal volume against age of onset of puberty defined as the recalled age at which pubic hair growth started. Note different y-axis scales. Significant correlations are indicated by the linear regression line. See text for more details.

Anthropometric variables

Current body weight and recalled body weight at 25 and 40 yr of age in early adult life were positively correlated with age-adjusted prostate volumes (Table 2 and Fig. 3). For example, the age-adjusted central, total, and peripheral prostate volume increased by 6.2, 4.9, and 3.9% per 10 kg of recalled body weight at age 25 yr. A similar pattern of correlation with predictive strength for central greater than total greater than peripheral prostate volumes was evident for age 40 yr (5.3, 3.4, and 2.4%) and current age (5.0, 3.9, and 3.4%), although the correlations based on the smaller numbers of data for recalled body weight at ages 14 and 50 yr were not significant.

TABLE 2. Relationship of anthropometric variables with age-adjusted prostate volumes

	n	Central		Total		Peripheral	
		r (*P*)	Coefficient (95% CI)	r (*P*)	Coefficient (95% CI)	r (*P*)	Coefficient (95% CI)
Weight (kg)							
14 yr old	221	0.107 (0.112)	1.0042 (0.999–1.0094)	0.122 (0.071)	1.0033 (0.999–1.0069)	0.111 (0.102)	1.0027 (0.999–1.0059)
25 yr old	322	0.155 (0.005)	1.0062 (1.0019–1.0107)	0.174 (0.002)	1.0049 (1.0019–1.0079)	0.158 (0.005)	1.0039 (1.0012–1.0065)
40 yr old	287	0.145 (0.014)	1.0053 (1.0011–1.0096)	0.133 (0.025)	1.0034 (1.0004–1.0063)	0.112 (0.059)	1.0024 (1.000–1.0050)
50 yr old	196	0.074 (0.302)	1.0033 (0.997–1.0096)	0.083 (0.254)	1.0024 (0.998–1.0066)	0.086 (0.234)	1.0021 (0.999–1.0056)
Current	399	0.148 (0.003)	1.0050 (1.0017–1.0082)	0.167 (<0.001)	1.0039 (1.0016–1.0062)	0.168 (<0.001)	1.0034 (1.0015–1.0054)
Height (cm)	399	0.177 (<0.001)	1.0119 (1.0053–1.0185)	0.231 (<0.001)	1.0108 (1.0063–1.0153)	0.233 (<0.001)	1.0095 (1.0056–1.0135)
BMI (kg/m^2)	399	0.080 (0.112)	1.0091 (0.998–1.0205)	0.071 (0.160)	1.0056 (0.998–1.0135)	0.068 (0.179)	1.0047 (0.998–1.0117)
BSA (m^2)	399	0.166 (<0.001)	1.4992 (1.182–1.901)	0.193 (<0.001)	1.389 (1.178–1.638)	0.193 (<0.001)	1.335 (1.156–1.543)
Lean mass (kg)	376	0.125 (0.016)	1.0070 (1.0013–1.0127)	0.167 (0.001)	1.0065 (1.0026–1.0105)	0.182 (<0.001)	1.0062 (1.0028–1.0096)
Fat mass (kg)	376	0.096 (0.062)	1.0052 (0.999–1.0107)	0.084 (0.103)	1.0032 (0.999–1.0070)	0.071 (0.169)	1.0023 (0.999–1.0057)
Hip (cm)	399	0.161 (0.001)	1.0100 (1.004–1.0161)	0.164 (0.001)	1.0071 (1.0029–1.0114)	0.152 (0.002)	1.0058 (1.0021–1.0095)
Waist (cm)	399	0.116 (0.021)	1.0049 (1.0008–1.0090)	0.111 (0.027)	1.0033 (1.0004–1.0062)	0.108 (0.032)	1.0028 (1.0002–1.0053)

Univariate relationships of anthropometric variables with age-adjusted central, total, and peripheral prostate volumes are tabulated as partial correlations (r, adjusted for age) with corresponding *P* values in *parentheses* below and of regression coefficients with their 95% confidence intervals (CI). The regression coefficients are back-transformed from the log scale in which prostate volumes were analyzed.

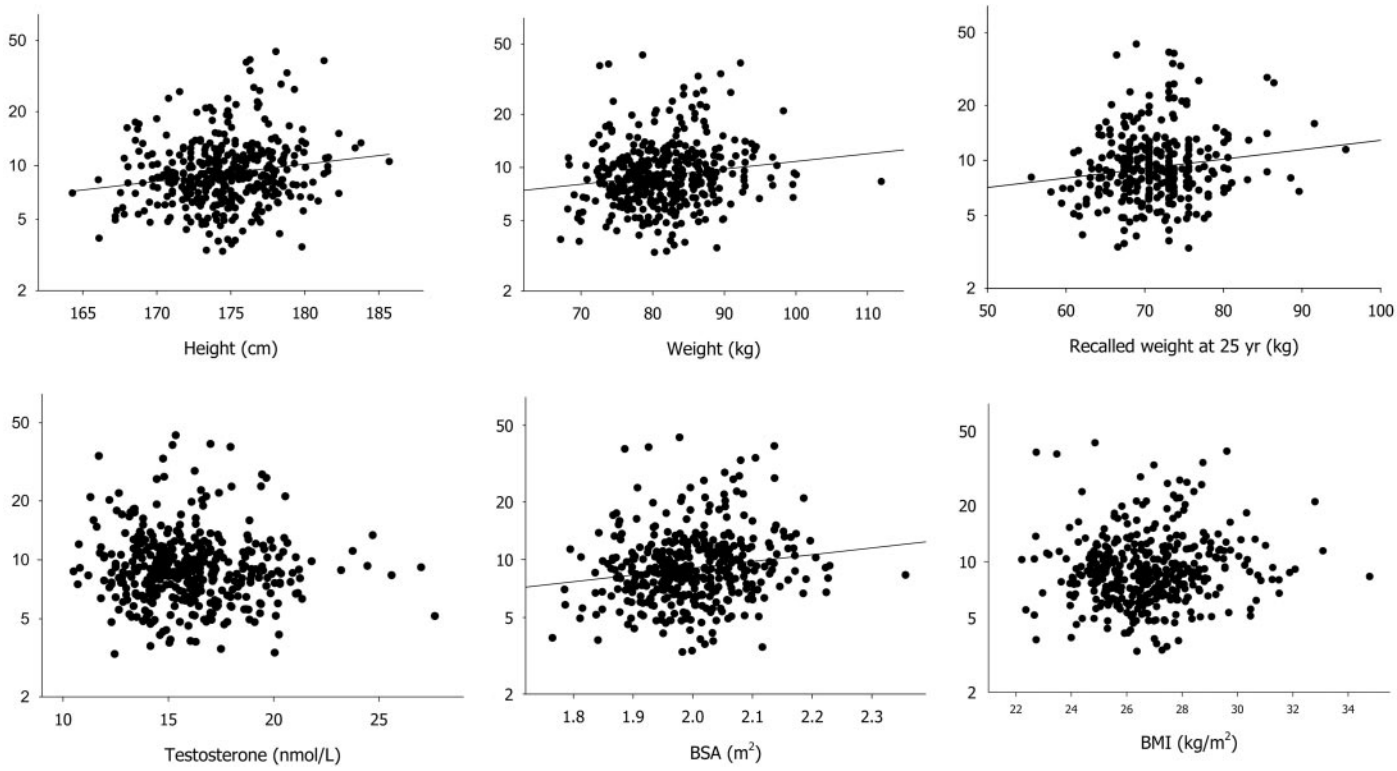

FIG. 3. Plot of central prostate volume against height, weight, recalled weight at age 25 yr, blood TT, BSA, and BMI. All plots are age adjusted. Note logarithmic scale on the y-axis. Significant correlations are indicated by the addition of a linear regression line.

Both current measured height and recalled height at age 14 were strongly predictive of prostate volumes (Table 3 and Fig. 3). Prostate volumes were significantly increased by 12% (central), 11% (total), and 10% (peripheral) per 10 cm of current body height. Compared with men who were of average height at age 14 yr, eventually taller boys had larger and shorter boys' smaller prostate volumes (Table 3).

BSA, lean body mass, and hip and waist circumference were all positively correlated with prostate volumes, whereas BMI, fat mass, and waist-to-hip ratio (not shown) were not. There were increases of 5.0% (central), 3.9% (total), and 3.4% per 0.1 m^2 of BSA; by 7.0% (central), 6.5% (total), and 6.2% (peripheral) per 10 kg of lean body mass; by 4.9% (central), 3.3% (total), and 2.8% (peripheral) per 10 cm of waist circumference; and by 10% (central), 7.1% (total), and 5.8% (peripheral) per 10 cm of hip circumference.

Among the anthropometric variables (age, height, weight, hip circumference, waist circumference, lean mass, fat mass, BSA, and BMI), forward and backward stepwise regression models (n = 376 men) produced a convergent final model including only age and height variables (both $P < 0.001$) in the best regression models for central ($R^2 = 0.341$), total ($R^2 = 0.293$), and peripheral ($R^2 = 0.218$) prostate volumes. Similarly, once adjusted for current age and height, the effects of recalled weight at ages 14, 25, and 40 yr were no longer significant (data not shown).

TABLE 3. Relationship of recalled height at age 14 yr on age-adjusted current prostate volumes

Height at 14 yr	n	Age-adjusted prostate volume (ml)		
		Central	Total	Peripheral
Taller	79	9.9 (9.0–10.9)	34.2 (32.1–36.5)	23.8 (22.5–25.2)
Average	248	9.1 (8.6–9.6)	31.3 (30.2–32.5)	21.9 (21.2–22.6)
Shorter	70	8.0 (7.3–8.9)	29.1 (27.2–31.1)	20.8 (19.6–22.1)

Age-adjusted current prostate volumes with 95% confidence intervals in *parentheses* are predicted by recalled height at age 14 yr when categorized according to whether taller, shorter, or similar to peers.

Hormones

As participants visited the study center throughout the day, blood was sampled from 0800–1800 h, and the exact time of sampling was recorded. For the whole study, the median time of sampling was 1125 h with 44% before 1000 h and 37% after 1400 h. Blood sampling time of day was inversely correlated to TT ($r = -0.15$; $P = 0.004$) and FT ($r = -0.18$; $P < 0.001$) but not to DHT, BT, SHBG, and estradiol($P > 0.3$). As a result, subsequent analyses involving blood TT or FT (but not other hormone variables) were adjusted for the time of blood sampling.

Age was correlated negatively with blood TT ($r = -0.265$; $P < 0.001$), FT ($r = -0.281$; $P < 0.001$), and BT ($r = -0.554$; $P < 0.001$) and positively with blood SHBG concentration ($r = 0.210$; $P < 0.001$) but not with DHT ($r = -0.061$) or estradiol ($r = 0.072$) after adjustment for time of day.

BMI was inversely correlated to TT ($r = -0.42$; $P < 0.001$), FT ($r = -0.20$; $P < 0.001$), DHT ($r = -0.23$; $P < 0.001$), BT ($r = -0.17$; $P = 0.001$), and SHBG ($r = -0.33$; $P < 0.001$) but not estradiol after adjustment for age and blood sampling time of day. Similarly, BSA was inversely correlated to TT ($r = -0.27$; $P < 0.001$), FT ($r = -0.11$; $P = 0.015$), DHT (r =

−0.17; $P = 0.001$), and SHBG (r = −0.32; $P < 0.001$) but not BT or estradiol after adjustment for age and blood sampling time of day.

Prostate volumes were inversely correlated with TT, FT, and BT but not significantly with DHT, SHBG, or estradiol (Fig. 3). When adjusted for age and sampling time of day (with or without height), the negative correlations with testosterone variables were all nullified (Table 4). Similarly, introduction of any hormone variables did not improve predictive models, which showed significant influence of weight at 14, 25, or 40 yr of age on age-adjusted prostate volumes (data not shown).

Discussion

After fetal growth and pubertal development, the prostate manifests a distinctive third growth phase commencing in mid-life and continuing throughout aging. This contrasts markedly with the involution of most organs during aging. The anatomical correlate of this late-life prostate enlargement is BPH, a nodular overgrowth originating anatomically in the central (or transitional) zone of the prostate (2). This progresses inexorably so that nearly all men who live out their life expectancy will develop BPH (1). Among those with this pathology, about half have LUTS so that BPH has a major impact on quality of life and is among the most frequent indications for surgery in older men. Although BPH is undoubtedly age (1) and androgen dependent (27), the mechanisms involved remain poorly defined. Many additional factors suggested by clinical or epidemiological research have often proved inconsistent between studies, at least partly because of the variable definitions (clinical, surgical, and pathological) of the clinical entity BPH (4, 27, 28). Yet, a hormone-dependent disorder with very slow progression and well-defined premorbid state should allow effective prevention if the pathogenesis were better understood.

This study examines the relationship between aging and anthropometric and hormonal variables as potential determinants of prostate size in middle and later life. Using an objective and continuous planimetric measure of prostate zonal volumes, it circumvents biases inherent in the categorical clinical or surgical diagnosis of BPH, which confound analytical research into its cause. Confirming previous findings, age was a strong determinant of prostate size as well as relevant explanatory hormonal and anthropometric variables. Key novel findings are that body growth and development during early manhood was an important predictor of mature prostate size and that the central prostate zone exhibited the strongest relationships with age and other predictor variables, followed by the total and then peripheral zones. Furthermore, when age effects were taken into account, the relationships between prostate zonal volumes with measured hormone variables were no longer significant. This indicates that apparent hormonal effects on prostate volumes could be accounted for by the positive effects of age on prostate size and its negative effects on blood testosterone and related hormonal variables.

A feature of the present study is the importance of timing of androgen-dependent body growth, and development during adolescence and early manhood were correlates of larger prostate size in later life. For example, age of pubertal onset, final height, and recalled weight at early age (14, 25, and 40 yr) were all independent determinants of mature prostate zonal volumes, after adjustment for current age. Yet, in stepwise multivariate regression, only current age and height remained significant independent predictors of prostate volumes. This indicates that these two variables effectively account for all correlations between anthropometric and hormone variables with prostate zonal volumes observed in this study.

Height predicts mortality from a variety of causes (29), including tall men having a higher risk of surgical BPH (30) or fast-growing BPH (31) and the metabolic syndrome (32), although better survival from prostate cancer is also reported (33). On the other hand, a comprehensive review of body size found no consistent relationship with height at diagnosis and prostate cancer (34, 35). These discrepancies may be the result of methodological differences and heterogeneity of prostate cancers by diagnosis and prognosis as well as a possibly genuine but relatively remote relationship with intervening nullifying variables. The negative correlation of height with age most likely represents an age-period-cohort effect, reflecting the generational changes in stature observed in many affluent countries in the latter half of the 20th century rather than actual height loss caused by spinal osteoporosis. Although this may reflect the general population, this nonsteady-state situation highlights another caveat on extrapolating empirical findings to the general population, regardless of sampling technique.

The stronger relationship of BSA than BMI in predicting prostate zonal volumes may be a result of the importance of height because BMI is a weight-for-height measure whereas BSA is an allometrically scaled product of height and weight. Previous studies of BPH have suggested relationships with obesity using BMI as a measure of adiposity. For example,

TABLE 4. Relationship of hormonal variables on raw and age-adjusted prostate zonal volumes

	n	Central		Total		Peripheral	
		Raw	Age-adjusted	Raw	Age-adjusted	Raw	Age-adjusted
TT (nmol/liter)	396	−0.201 (<0.001)	−0.061 (0.231)	−0.179 (<0.001)	−0.047 (0.356)	−0.154 (0.002)	−0.040 (0.425)
FT (pmol/liter)	392	−0.136 (<0.001)	0.036 (0.476)	−0.151 (0.003)	−0.002 (0.975)	−0.156 (0.002)	−0.036 (0.484)
BT (nmol/liter)	392	−0.322 (<0.001)	−0.006 (0.911)	−0.278 (<0.001)	0.007 (0.894)	−0.224 (<0.001)	0.011 (0.829)
DHT (nmol/liter)	343	0.001 (0.982)	0.047 (0.382)	0.004 (0.935)	0.044 (0.421)	−0.006 (0.905)	0.024 (0.664)
Estradiol (pmol/liter)	300	0.063 (0.275)	0.031 (0.595)	0.061 (0.295)	0.032 (0.586)	0.041 (0.482)	0.014 (0.809)
SHBG (nmol/liter)	396	0.077 (0.124)	−0.050 (0.319)	0.085 (0.092)	−0.024 (0.635)	0.077 (0.124)	−0.010 (0.843)

Relationship of central total and peripheral prostate volumes with hormone variables tabulated as raw and age-adjusted linear correlations with *P* values in *parentheses* below. TT and FT correlations are also adjusted for sampling time of day.

BMI was reported to be negatively correlated with surgically treated BPH in cohort studies (36–38), consistent with an earlier study of a graded decrease in relative risk of BPH in obese men (39). On the other hand, BMI was positively associated with prostate volume measured by transrectal ultrasound in African-American men (40). High BMI was positively correlated with prostate weight from transurethral prostatectomy in some (41, 42) but not other studies (43, 44). The present study raises the question of whether these relationships with body size would be clearer using BSA, which was not reported in any of these studies.

Although BMI has long been favored over body weight for clinical and epidemiological studies as a convenient proxy measure of adiposity in making allowance for body frame (34), it has well-known limitations (45). We have used more specific measures of body composition, such as measurement of lean and fat mass as well as of regional fat mass such as waist and hip circumference, to focus on how body size and composition may influence prostate pathology. Our data suggest lean body mass rather than adiposity was more strongly associated with prostate size. Lean body mass may be related indirectly to prostate size as a reflection of common relationships to circulating blood androgens because muscle is androgen dependent throughout life (46–48). However, with progressive aging, the decreased lean and increased fat mass may override this relationship. The present findings differ from those of a large prospective cohort study among health professionals where abdominal fat estimated by waist circumference was significantly associated with both surgical BPH and severity of LUTS whereas hip, waist-to-hip ratio or BMI were not (44). This discrepancy may be a result of the surgical definition of BPH and the additional nonprostate causes of LUTS whereas in this study prostate size was measured directly. These findings may also be reconciled between studies if obesity influences the impact and/or access to surgery for LUTS.

The positive predictive effects of recalled body weight during early adult life and the negative relationship with age of pubertal onset suggest the timing of early androgen exposure may influence mature prostate size. Analogous effects of delayed puberty are reported whereby late onset of growth spurt and acne were protective for histological diagnosis of prostate cancer (49). Androgen effects on growth at adolescence are complex. Muscle mass is strongly proportional to androgen exposure at all ages in men (46, 47). The increased muscularity during male puberty, forming the bulk of nonfat mass in younger men may explain the predictive effects of weight at early ages (14 and 25 yr) on mature prostate size. At later ages, however, the progressive increase in the less androgen-sensitive fat mass may attenuate the relationship between body weight and prostate size. Furthermore, during adolescence, accelerated bone growth in response to pubertal androgen surge causes the growth spurt to attain final height (50). However, statural growth is also curtailed by epiphyseal closure, which is precipitated by the pubertal increase in blood testosterone, probably via aromatization to estradiol in epiphyseal bone.

By contrast, the apparent relationship between current androgen exposure as measured by blood testosterone and its derivatives was negatively correlated with prostate volumes. This reflects the well-known juxtaposition that the age-related decline in blood testosterone (51) is accompanied by a progressive increase in prostate volume with age (1). However, when adjusted for current age, the relationship of the hormonal variables was nullified. This suggests that androgen effects on late-life prostate growth are indirect, possibly through effects at an earlier epoch of life together with progressive aging. This indirect relationship may explain discrepancies between the present findings and those of another study examining prostate zonal volumes where serum testosterone was significantly lower in men over 50 yr old with larger total and peripheral prostate volumes than those with smaller prostates (52), although that study did not detect a similar relationship with central volume. Other studies found no association between blood testosterone concentrations and BPH identified by clinical criteria (37, 43, 53).

The lack of relationship between blood DHT and prostate zonal volumes in this study may reflect the independence of intraprostatic DHT levels formed by local conversion of incoming testosterone from the bloodstream to DHT by the prostatic type 2 5α-reductase (54). This contrasts with a previous study of Chinese migrants as well as Chinese and non-Chinese Australian men where blood DHT levels reflected prostate size (11). It is possible that ethnogenetic differences in regulation of prostatic type 2 5α-reductase may have been underestimated in that study.

A strength of this study was the use of an objective ultrasonic measure of prostate size. Using a planimetric approach that provides a highly accurate and reproducible measurement of prostate zonal volumes overcomes a major limitation of previous clinical and epidemiological studies using either clinical (symptoms or digital rectal examination) or surgical (prostatectomy) as a categorical criterion for diagnosis of BPH. These diagnostic criteria for BPH are subject to significant ascertainment (referral, recruitment, and participation) bias as well as detection bias from the insensitivity of digital rectal examination. By contrast, the objective measure of prostate size as a continuous variable with findings not known to the participant when providing medical history details avoids the recall bias that contributes to the inconsistency of many factors identified in previous clinical and epidemiological studies of BPH.

An important limitation of the present study is that the study population was not randomly selected and hence not representative of the population from which it was drawn. A convenience sample, subject to self-selection bias, was unavoidable to get adequate participation for a study requiring an invasive procedure (transrectal ultrasound) in otherwise healthy men. A population-based, representative sample might have involved high rates of refusal to participate, such as seen in studies of young men requiring semen analysis (55–58), which can equally undermine valid generalization of findings. Hence, relationships that are valid within this study population may or may not be valid when extrapolated to the general male community. Nevertheless, the age-specific prevalence of LUTS in the current study population is similar to other international community studies (59, 60) where study populations are more representative. We conclude that early-life androgen-dependent growth and development should be considered as a potential determi-

nant of prostate zonal volumes and their hormonal or anthropometric correlates in future prospective and mechanistic studies.

Acknowledgments

We are grateful to the staff of the Department of Andrology, Concord Hospital (formerly Andrology Unit, Royal Prince Alfred Hospital), for their professional care and skill in facilitating the subject management for this study.

Received May 31, 2005. Accepted August 22, 2005.

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This study was partly funded by the National Health and Medical Research Council.

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