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Effects of Liver Disease and Transplantation on the Human Prostate

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ABSTRACT: A major determinant of late-life prostate diseases is hormonal exposure during earlier life, but the effects of androgens in midlife on the human prostate have been little studied. In order to identify hormonal effects on the prostate during the long latent period of midlife, we studied the effects of chronic androgen deficiency on the prostate during midlife by examining men with severe liver disease before and after liver transplantation. Patients (n = 15, median 57, range 38–65 years old) with severe liver disease but no known prostate disease being evaluated for liver transplantation underwent 21 prostate ultrasound studies, 12 prior to and 9 after liver transplantation, with six men undergoing both studies. Controls were 42 prostate ultrasound studies (2:1 matching) from age-matched healthy men. Total- and central-prostate volumes were measured with a 7.5-MHz biplane transducer planimetrically at 2.5-mm intervals with a stepper device from base to apex of the prostate. Overall, total- and central-prostate volumes were not significantly different between patients with chronic liver disease before and after liver transplantation and age-matched healthy controls. This appeared to be due to a bimodal distribution, with most men (12 men, 17 studies) having smaller prostate volumes and a minority (3 men, 4 studies) having previously undiagnosed, macroscopic, benign prostatic hyperplasia. The reduction in prostate volume prior to transplantation was significantly correlated with severity of liver disease (Child-Pugh score). Before liver transplantation, prostate-specific antigen (PSA) concentrations were significantly lower and prostatic acid phosphatase increased, and both were normalized after liver transplantation. Plasma testosterone concentrations were decreased before transplantation and remained low after transplantation. Sex hormone–binding globulin level was significantly elevated before and reduced to subnormal after liver transplantation. Estradiol concentrations were unchanged by liver disease or transplantation. We conclude that prostate volumes, particularly that of the central zone, are usually reduced by the functional androgen deficiency of chronic liver disease and tend to be restored toward normal by liver transplantation, depending on the degree of rectification of circulating plasma testosterone concentrations. Prostate glands with established benign prostatic hyperplasia may be less responsive to these hormonal changes.

Key words: Chronic liver disease, prostate ultrasound, androgen, estrogen.

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Prostate disorders such as benign prostatic hyperplasia (BPH) and prostate cancer are remarkably common among older men throughout the world, yet their pathogenesis remains poorly understood. The best characterized determinants of late-life prostate disease are age (Berry et al, 1984), androgen exposure in earlier adult life (Wu and Gu, 1987), and genetic factors (Partin et al, 1994; Meikle et al, 1997a,b). While the effects of age and genetics per se are difficult to modify, the hormonal dependence of the developing and aging prostate is susceptible to effective therapeutic interventions. Hence, deeper understanding of the hormonal determinants of prostate diseases is not only of theoretical scientific interest but also of practical strategic importance to prevention and improved treatment of prostate diseases as part of public health measures to promote healthy aging.

The prostate is a prime androgen target organ. Prostate growth and development is fully androgen-dependent at all epochs of life. Congenital defects in androgen action, such as mutations in the androgen receptor (Quigley et al, 1995) or the 5α-reductase type II enzyme (Imperato-McGinley et al, 1992) or castration in early life (Wu and Gu, 1987) impede prostate growth, leading to prostate development varying from nil to minimal. This vestigial development is generally believed to connote a reduced propensity to late-life prostate diseases (Moore, 1944). At the other end of the age spectrum, circulating androgen levels do not predict the subsequent development of prostate diseases over at least the decade prior to clinical diagnosis of disease (Nomura et al, 1988; Gann et al, 1996). Hence, very long-range, but not short-range, androgen action is an important determinant of late-life prostate disease. In this context, the relationship of androgen levels during the long latent period of the middle years of life before onset of overt clinical prostate disease remains unclear and has been little studied.

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One approach to studying the hormonal dependence of prostate diseases during the long latent period is to examine the effects on the prostate of variations in hormonal exposure due to chronic medical disorders associated with reduced androgen secretion. Chronic liver disease is associated with hypothalamic–pituitary gonadal dysfunction (including decreased testicular androgen secretion), which may be rectified by successful liver transplantation. Autopsy studies suggest that hepatic cirrhosis may be associated with a reduced prevalence and/or delayed onset of BPH (Guess, 1992; Boyle, 1994). A recent study demonstrated that hepatic cirrhosis was associated with decreased prostate volume and PSA (prostate-specific antigen) concentrations, which were proportional to the severity of underlying liver disease and predominantly determined by the decrease in circulating testosterone concentrations (Cetinkaya et al, 1998). Using the technique of planimetric ultrasound as the most accurate method to quantitate prostate size (Jin et al, 1996) and aiming to visualize the central zone of the prostate, as its most hormonally sensitive region, (Habenicht and El-Etreby, 1988), this study aimed to clarify the effects of chronic liver disease and liver transplantation on zonal prostate size and its hormonal determinants in comparison with healthy, age-matched controls.

Material and Methods

Subjects

Men over the age of 18 years with severe, terminal, chronic liver disease and undergoing evaluation for potential liver transplantation through the National Liver Transplant Unit, Royal Prince Alfred Hospital, were recruited for this study. Men with anorectal disorders or risk of atraumatic bleeding that posed unacceptable safety risk were excluded. Healthy age-matched controls were recruited from ongoing population-based studies of prostate volume conducted by the Andrology Unit, Royal Prince Alfred Hospital. None of the controls had any history of significant liver disease. The study was approved by the Human Ethics Review Committee of the Central Sydney Area Health Service (RPAH Zone), and participants were required to provide written, informed consent.

All participants underwent a standardized medical history; physical examination, including a digital rectal examination to exclude significant anorectal disease; and provided a blood sample for measurement of PSA, acid phosphatase, reproductive hormones (LH [luteinizing hormone], FSH [follicle-stimulating hormone], total and free testosterone, estradiol, and SHBG [sex hormone–binding globulin]), and biochemical liver function tests. Blood samples were always taken prior to the prostate ultrasound procedure.

Prostate Ultrasound

Prostate ultrasound was performed with OPUS 1 (AUSONIC, Sydney, Australia) real-time B-mode ultrasound equipment with a 7.5-MHz biplanar transrectal transducer (2 cm external diameter). The ultrasound transmission gel (AQUASONIC, Parker Laboratories, New Jersey) was applied to the transducer, which was then covered with a disposable rubber sheath. The lubricated transducer is inserted gently and gradually about 3–5 cm into the rectum and directed toward the anterior rectal wall in order to visualize the whole prostate, which is then scanned in the transverse and sagittal planes separately. Each prostate ultrasound procedure took an average of 10 minutes (range, 5–15 minutes). All prostate ultrasounds and calculations were performed by the same observer (B.J.).

Total- and central-prostate volumes were measured by planimetry and the ellipsoidal model, using frozen cross-sectional images. Cross-sectional areas of each slice of the prostate were measured sequentially from base to apex at 2.5-mm intervals with a calibrated stepper device. At each step, the two-dimensional sonographic image of the prostate was outlined manually with a track ball, and the image was integrated automatically to give the slice's cross-sectional area. In addition, the three maximal diameters of the prostate were measured for both total and central areas of the prostate. Subsequently, prostate volume was calculated by reconstruction of all planimetric sections as well as from the standard ellipsoidal formula using the three maximal dimensions measured. All results of ultrasound were recorded by the video processor (P67E, Mitsubishi) and video cassette machine. The sonographic central-prostate volume includes the anatomical areas of the transitional zone, central zone, and anterior fibromuscular stroma, according to the zonal description of McNeal (McNeal, 1978, 1983). Periperal-prostate volume was calculated as the difference between the total- and central-prostate volumes.

Assays

Total and free testosterone, estradiol, LH, FSH, SHBG, and PSA were measured by standard immunoradiometric assays performed within the laboratories of the Royal Prince Alfred Hospital and University of Sydney as described previously (Handelsman et al, 1990, 1995, 1996).

Data Analysis

Age-matched controls (2:1 ratio) were selected from volunteers in the ongoing survey of prostate size of healthy eugonadal men. Data were expressed as mean and standard error of the mean unless otherwise stated and were analyzed by unpaired *t*-test or by the nonparametric equivalent test if the data were nongaussian, giving exact *P* values.

Results

Study Population

Fifteen men with liver disease for a median duration of 9 (range 1–30) years undergoing evaluation for liver transplantation were studied. None were known to have prostate disease prior to entry to the study. The causes of chronic liver disease were postviral hepatitis (eight subjects), primary sclerosing cholangitis (two subjects), cryp-

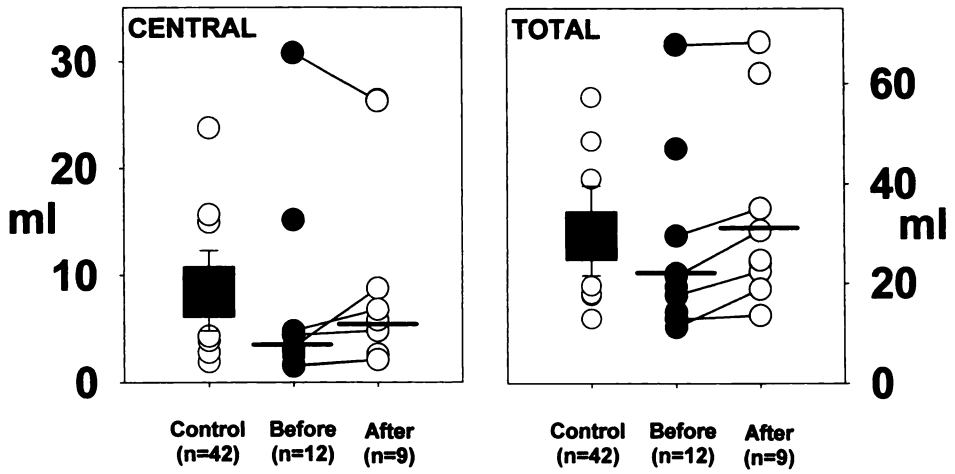

FIG. 1. Box-and-whiskers plots of central- (left panel) and total- (right panel) prostate volume in milliliters among men with chronic liver disease before (n = 12) and after (n = 9) liver transplantation. Lines join the six men who underwent examinations before and after liver transplantation.

togenic cirrhosis (two subjects), and alcoholic liver disease (three subjects). The severity of liver disease was categorized by Child-Pugh score (Pugh et al, 1973) as class A in one, class B in five, and class C in six men before liver transplantation. The study included 21 examinations comprising 12 procedures (median age 55, range 38–65 years) prior to transplantation and 9 (median age 60, range 38–62 years) after transplantation. Six men had both pre- and posttransplant examination, with the latter occurring at a mean of 4 (range 3–6) months after liver transplantation. Prior to transplantation, men with severe liver disease had lower body weight (74.2 ± 2.4 vs. 83.5 ± 2.4 kg, P = 0.02) and body surface area (1.9 ± 0.03 vs. 2.0 ± 0.03 m^2, P = 0.04) but similar height, body mass index, and testis volumes compared with their age-matched healthy controls. After transplantation, height, weight, body mass index, body surface area, and testis volumes were similar to those of age-matched healthy controls. The control group consisted of 42 age-matched men (2:1 ratio) recruited from a concurrent study of prostate volumes in healthy men.

The other medical conditions among men with chronic liver diseases were hypertension (five subjects), diabetes mellitus (three subjects), ulcerative colitis (two subjects), polycythemia (one subject), and renal transplant (one subject). Concomitant medication used by more than one patient included spironolactone (n = 7; median dose 150 mg/day, range 50–300 mg), frusemide (n = 4; median dose 180 mg/day, range 120–240 mg), omperazole (n = 4; median dose 15 mg/day, range 10–20 mg), and ranitidine (n = 3; median dose 220 mg/day, range 150–300 mg). Standard immunosuppressive medication after transplantation included prednisone (median dose 7.5 mg/day, range 5–10 mg/day), cyclosporin A (median dose 300 mg/day, range 200–500 mg/day), and azathioprine (median dose 50 mg/day, range 0–75 mg/day).

Prostate Volumes

Overall total-, central-, and peripheral-prostate volumes were not statistically different between men with severe chronic liver diseases before (P = 0.09) or after liver transplantation or in comparison with healthy age-matched controls. There was, however, striking heterogeneity between patients with chronic liver disease with a distinctly bimodal distribution of prostate volumes (Fig. 1). Most men had smaller central- and total-prostate volume before transplantation with an increase after transplantation. In addition, there were also extreme values that may have been outliers (Fig. 1). These corresponded to three men, aged between 57–62 years, in each of whom the ultrasound demonstrated diffuse hyperechoic images with multiple calculi, consistent with the diagnosis of BPH. One of these three men had very large prostate volumes before and after transplantation, whereas the other two had large prostate volumes, in one case before and the other after transplantation, but they were only available for study on one occasion each. Among the six men studied before and after transplantation, prostate volumes increased by 18% in total, 10% in central, and 21% in peripheral volumes, but none of these changes was statistically significant. Prior to liver transplantation, the Child-Pugh score was strongly correlated with total (P = 0.03) and central (P = 0.03) volumes of the prostate (Fig. 2).

Blood PSA concentration was significantly lower before liver transplantation (0.3 ± 0.2 vs. 1.4 ± 0.4, P = 0.02) but was comparable with healthy controls after liver transplantation (Fig. 2). Prostatic acid phosphatase was significantly higher (2.0 ± 0.4 vs. 1.2 ± 0.1, P = 0.02) before transplantation but was comparable with that of healthy age-matched controls after liver transplantation.

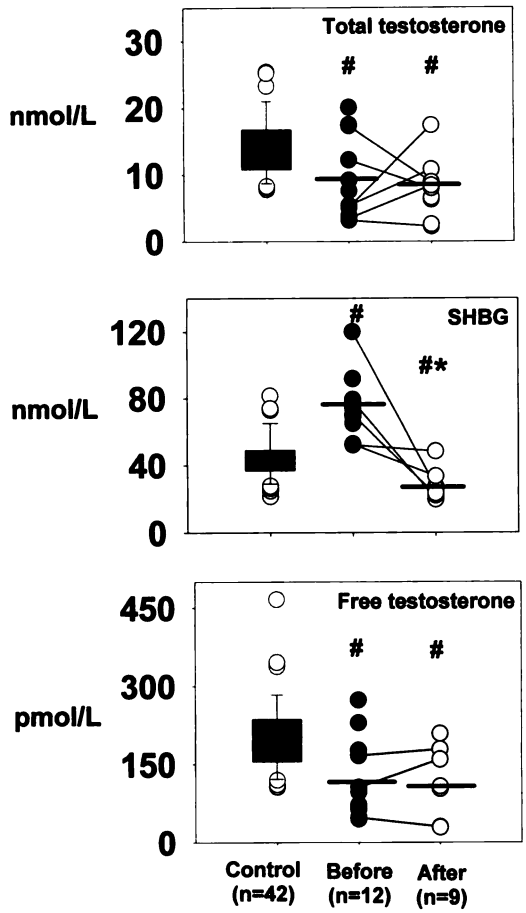

FIG. 2. Scatter plots show the correlation between central-prostate volume (left panel) and total-prostate volume (right panel) with the Child-Pugh score in men before liver transplantation (n = 12). The linear correlation coefficient and the P-value for the regression are indicated.

Hormones

Total- and free-testosterone concentrations were significantly lower in patients with chronic severe liver diseases before transplantation and remained lower than those of age-matched healthy controls after liver transplantation (Fig. 2). Neither total nor free testosterone were correlated with total-, central-, or periperal-prostate volumes. Sex hormone–binding globulin levels were markedly increased before transplantation and then decreased to subnormal levels after transplantation. Serum estradiol level was unchanged by the presence of severe liver disease or by liver transplantation (Fig. 3). Plasma LH level was increased in liver disease and rose further after liver transplantation. Plasma FSH levels were nonsignificantly elevated before and after liver transplantation, without significant change due to liver transplantation. Testicular volume was unaffected by liver disease or transplantation.

Liver Function

Biochemical tests of liver function were abnormal prior to liver transplantation and were improved by liver transplantation. Improvement in plasma albumin was correlated inversely with SHBG (r = −0.60, P = 0.007) and estradiol (r = −0.68, P = 0.002) concentrations but not with prostate volumes or other hormone concentrations among men with liver disease (Fig. 4).

Discussion

The present study has characterized the total, central, and peripheral volumes of the prostate by planimetric ultrasound as well as their hormonal determinants in men with chronic liver disease before and after liver transplantation in comparison with age-matched healthy control men. Blood PSA concentration was lower in men with chronic

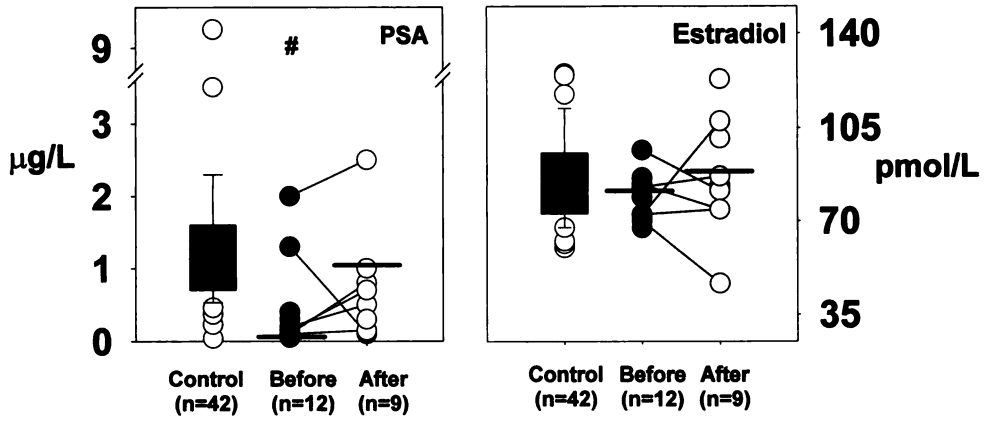

FIG. 3. Box-and-whiskers plots of plasma total-testosterone (top panel), SHBG (middle panel), and free-testosterone (lower panel) concentrations in men with chronic liver disease before (n = 12) and after (n = 9) liver transplantation. Lines join the six men who underwent examinations before and after liver transplantation. The hash (#) symbol indicates a significant difference from the controls, and the asterisk symbol (*) indicates a significant difference for patients after, compared with before, liver transplantation by paired t-test.

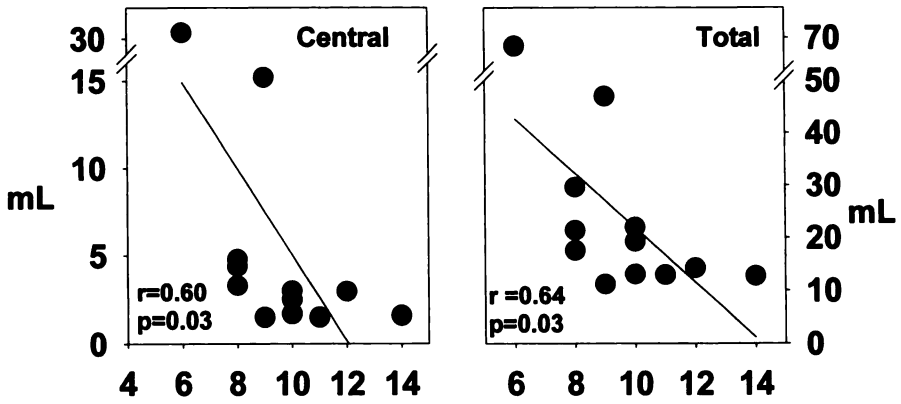

FIG. 4. Box-and-whiskers plots of plasma PSA (left panel) and estradiol (right panel) concentrations in men with chronic liver disease before (n = 12) and after (n = 9) liver transplantation. Lines join the six men who underwent examinations before and after liver transplantation. The hash (#) symbol indicates significant difference from the controls.

liver disease before transplantation than in age-matched healthy controls, whereas PSA was normalized after transplantation. Prostate volumes appeared to be bimodally distributed. Most men with chronic liver disease prior to transplantation had smaller central- and total-prostate volumes, whereas prostate volumes were a little higher in men after liver transplantation. A minority of men had pathological prostatic enlargement due to benign prostatic hyperplasia, which may have predated the liver disease. Prostate enlargement in these men was largely unresponsive to hormonal changes associated with liver disease or transplantation.

Previous studies of the prostate in liver disease have included postmortem examinations on men who died of hepatic cirrhosis (Wu, 1942; Bennett et al, 1950; Stumpf and Wilens, 1953; Robson, 1966; Frea et al, 1987) and an ultrasound study that examined the prostate in men with chronic liver disease during life (Cetinkaya et al, 1998). No previous studies have examined prostate morphology after liver transplantation. Recent reviews of the epidemiology of BPH have suggested that such observations warranted further rigorous clinical study (Guess, 1992; Boyle, 1994). Among the five postmortem studies of prostate morphology among men dying of chronic liver disease, four have suggested that chronic liver disease was associated with a diminished and delayed onset of BPH in which stromal hyperplasia was particularly prominent (Bennett et al, 1950; Stumpf and Wilens, 1953; Robson, 1966; Frea et al, 1987), whereas one study showed no difference in prevalence of BPH (Wu, 1942). The latter study may be discrepant because of its reliance on a small, selected, and possibly unrepresentative sample of patients with liver cirrhosis who were compared with historical rather than contemporary controls. A recent study of 60 men with postnecrotic and alcoholic cirrhosis has shown reduced total-prostate volume calculated using an ellipsoidal approximation that was correlated with disease severity and reduction in circulating testosterone concentrations (Cetinkaya et al, 1998). The present study was based on the premise that men with severe liver disease should have reduced prostate size on the basis of their state of androgen deficiency and that prostate volume may increase after a successful liver transplant. In addition, previous studies have been in men with predominantly alcoholic liver disease, thereby introducing the confounding effects of direct alcohol toxicity and associated malnutrition, whereas this study had only a minority with alcoholic liver disease.

The effects of chronic liver disease and transplantation changes on prostate structure and function are presumably hormonal in origin. The changes in prostate volumes and PSA secretion appeared most closely related to changes in plasma testosterone. In the present study, estradiol concentrations were unchanged by severe liver disease or transplantation, a finding that is consistent with some but not all previous studies of liver disease and transplantation. This makes it unlikely that the changes in prostate volumes related to liver disease and transplantation are mediated by changes in estradiol. Similarly, SHBG concentrations were grossly elevated (70% above normal) in men with severe liver disease and then fell to subnormal (38% below normal) after liver transplantation. The latter finding may contribute to the apparent failure of plasma testosterone to increase after liver transplantation, confirming our previous observation (Handelsman et al, 1995). The endocrine findings in men with chronic liver disease in this study (a decrease in plasma total and free testosterone, unchanged estradiol, and increased plasma SHBG concentrations) are consistent with the characteristic features of hypothalamic–pituitary testicular dysfunction in chronic alcoholic liver disease (van Thiel et al, 1981, 1990; Bannister et al, 1987; Gluud, 1988; Handelsman et al, 1995). The effects of nonalcoholic liver disease (van Thiel et al, 1981; Bannister et al, 1987; Han-

delsman et al, 1995) and of liver transplantation (van Thiel et al, 1990; Guechot et al, 1994; Madersbacher et al, 1994, 1996; Handelsman et al, 1995) have been less studied. In general, alcohol appears to have independent testicular toxicity, and the changes due to liver failure are largely reversed with successful liver transplantation. The low proportion of alcohol-induced liver disease among our study population is therefore unlikely to have been a major contribution to the failure of plasma testosterone concentrations to increase after liver transplantation. It is quite plausible that the chronic androgen deficiency of severe liver disease may explain a reduction in prostate volumes and PSA, such as that observed in most younger men with liver failure, as well as its limited reversibility after liver transplantation. In addition, a minority of the oldest men with liver disease may have already developed BPH that continues to grow autonomously despite the hormonal-deficiency state of chronic liver disease. It is possible that if plasma testosterone concentrations had increased more after liver transplantation, then prostate regrowth may have been even more marked. Caveats on the interpretation of this study include the fact that the sample size is relatively limited, which may have led to unrecognized and unintended bias in sample selection. In addition, drug treatments for liver disease may have confounding effects on the endpoints of the study, as exemplified by the effects of spironolactone, which is frequently used in treatment of advanced liver disease but which may have estrogenic hormonal side effects (McDonald et al, 1993; Handelsman et al, 1995).

We conclude that prostate volume is influenced by severe liver disease and that these effects are reversed after liver transplantation. The pathogenesis of these changes appears to be via chronic androgen deficiency before transplantation and its rectification by successful liver transplantation. These changes indicate that the healthy human prostate gland during midlife remains responsive to modulation by changes in systemic androgen exposure, although after onset of BPH, the morphological and secretory changes may be diminished.

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