Prostate health and male hormones

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Andropause has a profound effect on prostate function, even though many mechanisms related to testosterone and prostate physiology are unclear. The most worrisome aspect in andropause evaluation is prostate cancer, which is an absolute contraindication for androgen treatment. Early detection of prostate cancer using prostate-specific androgen (PSA) measurement and digital rectal examination (DRE) findings should be offered to men at high risk (those with a positive family history and/or of African-American ethnic background) who are older than 40 years of age and who have at least a 10-year life expectancy (22). Patients contemplating testosterone replacement therapy should have prostate screening (DRE and PSA measurement) before initiating therapy and then at six-month intervals. Men with abnormal DRE or PSA findings, or those with the presence of prostatic intraepithelial neoplasa on biopsy are not suitable for this treatment.

Key Words: *Prostatic carcinogenesis; Prostatic hormones; Serum markers; Digital rectal examination; Prostate biopsy; Prostate-specific antigen testing*

Santé de la prostate et hormones mâles

RÉSUMÉ : L'andropause produit un effet marqué sur le fonctionnement de la prostate, même si bon nombre de mécanismes liés à la physiologie de la testostérone et de la prostate restent encore nébuleux. Le trouble le plus grave à relever au cours de l'évaluation de l'andropause est le cancer de la prostate, qui constitue une contre-indication absolue au traitement aux androgènes. Les hommes à risque élevé (antécédents familiaux ou ascendance afro-américaine) qui ont plus de 40 ans et qui ont une espérance de vie d'au moins 10 ans (22) devraient être soumis à un dépistage précoce du cancer de la prostate par une mesure des androgènes spécifiques de la prostate (ASP) et par le toucher rectal (TR). Les patients qui désirent l'hormonothérapie substitutive aux androgènes devraient faire l'objet de dépistage du cancer de la prostate (ASP et TR) avant l'amorce du traitement, puis aux six mois. Les hommes qui ont des résultats anormaux aux tests de dépistage et ceux qui présentent des cellules néoplasiques intraépithéliales prostatiques à la biopsie ne sont pas candidats à cette forme de thérapie.

PROSTATIC CARCINOGENESIS AND HORMONES

The etiology of carcinoma of the prostate is unclear; however, several risk factors, such as race, positive family history (1) and diet, have been identified. The disease is more common in black than white men (2). A diet rich in fructose and low in calcium promotes the hydroxylation of vitamin D, which has antitumour properties (3). An increased intake of vegetables, especially tomatoes, is inversely associated with the incidence of prostate cancer (4). Selenium intake also has a protective property against prostate cancer (5). Soy protein, which is a phytoestrogen, has an estrogen-like effect on the prostate (6).

Androgen receptors (AR) are widely present in the prostate and are normally activated by androgen binding. In the prostate, types 1 and 2 5-alpha-reductases convert testosterone to dehydrotestosterone. The dehydrotestosterone-AR complex is more stable than the testosterone-AR complex. Androgens may influence serum prostate-specific antigen

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TABLE 1
Age-adjusted, prostate-specific androgen values by ethnic group

	Reference range (ng/mL)		
Age range (years)	Asian men	Black men	White men
40 to 49	0 to 2.0	0 to 2.0	0 to 2.5
50 to 59	0 to 3.0	0 to 4.0	0 to 3.5
60 to 69	0 to 4.0	0 to 4.5	0 to 4.5
70 to 79	0 to 5.0	0 to 5.5	0 to 6.5

Data from reference 16

(PSA) levels, increase prostate size and obstructive symptoms, and activate occult prostatic malignancy (7). In clinical settings, these changes are very minimal and not statistically different from those in untreated hypogonadal men (8). There is no evidence to date that serum sex hormones promote prostate cancer (9). The above observation is, however, based on short term observations (of up to three years of follow-up), and hence, prostate cancer has a long, natural history in which the role of androgens in the activation of prostate cancer remains unclear.

Castration results in the involution of the prostate and apoptosis. Androgen-deprivation therapy decreases PSA and testosterone levels. The effect on serum testosterone extends beyond the cessation of treatment and may last as long as seven months (10). Estrogens modulate androgenic effects on prostate tissue and decrease serum testosterone levels (11).

Apoptosis and tumour suppressor genes are now considered to be the primary mechanisms of prostate cancer development (12), and genes such as Tp53, $p21^{WAF1/CIP1}$, Bcl-2, PTEN/MMAC1 and p73 have been implicated in the pathogenesis of prostate cancer.

SERUM MARKERS AND DIGITAL RECTAL EXAMINATION

PSA testing was introduced into clinical practice in the 1980s and has dramatically changed the management of prostate cancer since then. It is an invaluable tool in the detection, staging and monitoring of prostate cancer. PSA analysis is the best single test for the detection of early prostate cancer. Using the upper limit of normal of 4.0 ng/mL, the PSA test has a sensitivity of 67.5% to 80% (13). Approximately 20% of all prostate cancer is found in men with PSA levels lower than 4.0 ng/mL (14). The probability of detecting prostate cancer is about 25% if the PSA level is 4 to 10 ng/mL (15). When the PSA level is greater than 10 ng/mL, the probability of cancer detection increases to 60%. To improve the detection of prostate cancer and avoid unnecessary biopsies, several different PSA tests, such as PSA density (PSA value/ volume of prostate), PSA velocity (greater than 0.75 ng/mL per year), age-specific PSA and transitional zone PSA density, have been suggested. Only the age-specific PSA reference range (Table 1) is clinically useful (16).

PSA exists in serum in either bound (complexed) or unbound (free) form. Free PSA ranges from 5% to 50% of total PSA. Patients with prostate cancer have a lower fraction of free PSA compared with the bound fraction. Men with total PSA levels between 4 to 10 ng/mL and ratios of free to total PSA greater than 20% to 25% have a significantly lower risk of prostate cancer on biopsy (17). The cut-off value of free to total PSA at 25% increases the sensitivity and specificity of detecting prostate cancer to 95% and 20%, respectively. In men with total PSA levels less than 4.0 ng/mL, the free PSA measurement is uncertain.

Prostate cancer, benign prostatic hypertrophy and prostatitis my cause PSA levels to rise. Physical activity, infection, urinary retention and some medications may also influence PSA levels. Prostatic needle biopsy and digital rectal examination (DRE) may cause a transient elevation in free and total PSA levels. Finasteride (Proscar, Merck Frosst Canada, Canada), a 5-alpha-reductase inhibitor, decreases PSA levels by 50% on average (18). Some herbal prostate compounds can also lower PSA levels.

Human kallikrein 2 is a newly discovered prostate marker in which 80% of amino acid sequences are identical to those of PSA (19). It is more prostate tumour-specific. Future clinical trials will show if this new marker is more useful.

The use of DRE results alone have a poor predictive value in the diagnosis of prostate cancer (16%) and considerably understage the extent of prostate cancer. DRE, however, has a large influence in combination with PSA and age ranges on the probability of positive biopsy (51%) (20,21).

Early detection of prostate cancer using PSA and DRE findings should be offered to men older than age 50 years, men at high risk (ie, those with a positive family history and and/or an African-American ethnic background) and men older than age 40 years who have at least a 10-year life expectancy (22).

Canadian Urological Association guidelines read: "The digital rectal examination (DRE) and prostate specific antigen (PSA) measurements increase the early detection of clinically significant prostate cancer. Men should be aware of the potential benefits and risks of early detection so they can make an informed decision as to whether to have this test performed".

PROSTATE BIOPSY

The only test that confirms the presence of prostate cancer is a prostate biopsy, which is usually performed using transrectal ultrasound (TRUS) guidance. Overall, the staging accuracy of solely using TRUS results is 58%. A TRUS biopsy is indicated if a patient has elevated PSA levels or an abnormal DRE result. Prostate biopsy may improve clinical staging. The number of biopsies that are needed for adequate sampling is still controversial, but sextant biopsy is now used in standard practice (23). Sextant biopsy, however, has a false-negative rate of 23% to 31% (24).

Prostatic intraepithelial neoplasia (PIN) is a pathological diagnosis of histological changes, which are abnormal but

not yet malignant. PIN has a high predictive value as a histological marker for prostate cancer. Prostate cancer has been diagnosed in 35% of men with PIN versus 13% of those in a control group (25).

CONCLUSIONS

Andropause has a profound effect on prostate function, even though many mechanisms related to testosterone and prostate physiology are unclear. The most worrisome aspect in andropause evaluation is prostate cancer, which is an absolute contraindication for androgen treatment. Patients contemplating testosterone replacement therapy should have prostate screening (DRE and PSA measurement) before initiating therapy and then at six-month intervals. Men with abnormal DRE or PSA findings, or those with the presence of PIN on biopsy are not suitable for this treatment.

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