PROSTATE-SPECIFIC ANTIGEN IN FEMALE URINE: A PROSPECTIVE STUDY INVOLVING 217 WOMEN

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ABSTRACT

Objectives. Histomorphologic studies have provided evidence of prostate-specific antigen (PSA)-producing tissue in the female urethra. Some urine samples from women in a small series were positive for PSA, but no systematic investigation of this subject has been done to date.

Methods. In a prospective study, we analyzed whether PSA occurs in the urine of women and what factors induce detectable PSA levels. The urine samples of 217 women were analyzed (Hybritech-Tandem E-PSA) under standardized conditions. The impact of urine pH and volume was investigated, and the results were correlated with clinical data (age, residual urine, urinary tract infection and prior sexual intercourse within 48 hours).

Results. A positive PSA level greater than the detection limit of 0.1 ng/mL was found in 11% of the analyzed samples; their mean value was 0.29 ng/mL. pH correction did not result in a significant difference. The voiding volume had no influence on the PSA level. Among the cases of detectable PSA, women younger than 50 years of age (n = 14) had a mean PSA of 0.34 ng/mL and those older than 50 years (n = 9) a mean of 0.23 ng/mL. One of 9 women with and 22 of 208 women without residual urine volume had a detectable PSA level, as did 0 of 20 with and 23 of 197 women without urinary tract infection, and 3 of 7 with and 20 of 210 women without prior sexual intercourse within the previous 48 hours. None of the differences were significant.

Conclusions. A urine PSA level was detected in 11% of all women studied, with PSA values apparently age dependent. Any urine portion is suitable for analysis. No influence was determined for residual urine volume or urinary tract infection. Sexual intercourse may cause detectable PSA values, but the data of this study did not provide sufficient evidence for this hypothesis.

MATERIAL AND METHODS

Urine samples of 217 consecutive women were analyzed for PSA values to determine what factors influence the PSA level. All women admitted to our clinic within a period of 5 months in 1998 were recruited. A minimum initial portion of morning urine (volume in milliliters) was analyzed with the Hybritech-Tandem E-PSA assay under the following standardized conditions: measurement in native urine (detection limit according to the manufacturer of 0.1 ng/mL or greater) and after pH...
correction. Test sets for PSA determination in urine were not commercially available. However, as Spitz et al.\textsuperscript{11} were able to demonstrate, the estimation of PSA in urine can be performed using a commercially available assay for serum specimens without loss in accuracy. No modification was necessary.\textsuperscript{11}

**LABORATORY TECHNIQUES**

The samples were stored for a maximum period of 2 weeks at $-20^\circ$C before measurement. All urine samples underwent agitation for mixing purposes, after which the pH was measured and 1 mL removed for PSA analysis. The remaining urine was titrated to pH 7.5, after which another sample was taken.

The correlation of the urine PSA values with pH, urine volume, age, residual urine volume, urinary tract infection and sexual intercourse within 48 hours before sampling was then determined in statistical terms. The distribution type of the measurements was assessed by the Kolmogorov-Smirnov test. To determine the significance of the correlation among urinary PSA, pH, and volume, the Wilcoxon-Mann-Whitney test was applied. Furthermore, the Fisher exact test was performed for statistical differences between the clinical subgroups.

**RESULTS**

PSA (greater than 0.1 ng/mL) could be detected in the urine of 23 (11%) of 217 women; the mean was 0.29 ng/mL (median 0.19, range 0.12 to 1.06) with an average urine pH of 6.2 (range 5.0 to 8.5). The mean PSA level in all native urine samples was 0.047 ng/mL (SD 0.08). Correcting the pH to pH 7.5 resulted in a change in urine PSA levels to 0.050 ng/mL (SD 0.11; difference not significant). The study parameters were thus clearly not pH dependent. The influence of volume of the spontaneous urine on urine PSA was also not significant. In volumes smaller than 50 mL, the average PSA level was 0.056 ng/mL (SD 0.12) (n = 94); at volumes of 50 mL or greater, the average PSA level was 0.058 ng/mL (SD 0.12) (n = 123). Nondetectable PSA values were regarded as 0.00 ng/mL. In terms of volume, 13 (14%) of 94 samples (mean PSA 0.222 ng/mL; volume less than 50 mL) and 10 (8%) of 123 samples (mean PSA 0.389 ng/mL; volume 50 mL or greater) were PSA positive. The average PSA concentration in the patient group with larger volumes exceeded the PSA concentration in the patient group with smaller volumes by a factor of 1.7, thus ruling out a dilution effect. The correlation between age and PSA (age range 18 to 74 years, mean age 43, median age 42) revealed a statistically insignificant tendency toward a reduction in PSA level with increasing age. Women younger than 50 years of age (n = 14) had a mean PSA level of 0.34 ng/mL (median 0.19); those older than 50 (n = 9) had a mean PSA level of 0.23 ng/mL (median 0.15). A PSA-positive result was obtained in 1 of 9 with and 22 of 208 without a residual urine volume, 0 of 20 with and 23 of 197 without urinary tract infection, and 3 of 7 women with and 20 of 210 women without prior sexual intercourse, all without statistical relevance.

**COMMENT**

In this study, PSA in female urine, along with the question of its dependence on various factors, was investigated systematically and prospectively in a large group of women for the first time. PSA was found in the urine of every ninth woman. Histologic analyses of the female urethra by several other investigators have provided evidence for the potential origins of such PSA-positive cases. Pollen and Dreilinger\textsuperscript{2} detected the presence of PSA-positive cells in 7 of 10 female periurethral glands by immunohistochemical methods in 1984. Wernert et al.\textsuperscript{1} found PSA-positive histologic features in two thirds of a collective of 33 women. Since the embryologic origin of the periurethral glands corresponds to that of the male prostate, a histomorphologic similarity is also probable.\textsuperscript{4} PSA expression was also detected in the urachal structures in autopsies of both men and women.\textsuperscript{3} A comparison with the few studies on PSA measurement in the urine of small collectives of women revealed varying results: Takayama et al.\textsuperscript{9} (n = 12) and Tremblay et al.\textsuperscript{6} found no PSA in female urine. Both Spitz et al.\textsuperscript{11} (n = 8) and Graves et al.\textsuperscript{3} (n = 15) detected no levels above the detection limit of 0.3 ng/mL and 3 ng/mL, respectively. De Vere White et al.,\textsuperscript{7} in contrast, detected an average level of 0.2 ng/mL PSA in 10 of 15 women, in which sexual intercourse was not taken into account. Breul et al.\textsuperscript{10} found PSA levels exceeding 0.5 ng/mL in one third of his collective (n = 34), averaging 3.72 ng/mL; the levels in women after sexual intercourse were clearly higher (31 ng/mL). In a recent study, Breul et al.\textsuperscript{12} detected an average level of 1.73 ng/mL in 20 women. Applying a sensitive test to our much larger collective of 217 women, we detected PSA in the urine of 11%. In these women, the average level (0.29 ng/mL) was considerably greater than the detection limit. This small percentage of PSA-positive urine samples was probably because we evaluated a nonselected collective.

As with Spitz et al.,\textsuperscript{11} and in contrast to the other investigators,\textsuperscript{7,9,10} we were also unable to determine any influence of pH shifts. pH correction appeared to be of no value for PSA measurement in urine.

In their studies of male patients, Takayama et al.\textsuperscript{9},\textsuperscript{9} Iwakiri et al.\textsuperscript{8} and Tremblay et al.\textsuperscript{6} concluded that PSA determination in first-stream urine samples leads to higher results. Likewise Spitz et al.\textsuperscript{11} also reported this tendency in their measurements of fractionated spontaneous urine in men. In their study, the first 40-mL portion was characterized by PSA concentrations about two to four times higher.
than those in subsequent urine fractions, except for the last portion, which showed a renewed increase. This evidence supports the hypothesis that PSA is produced by the periurethral glands in the distal urogenital tract, where it is flushed out by the urine. In this manner, a dilution effect, as Spitz et al. have found, can be expected. The increase of PSA in the last portion is interpreted as being due to the muscle contraction of the bladder neck and urethra at the end of voiding.11 According to the hypothesis that PSA is produced by the periurethral glands, it was confirmed in studies of renal fistular urine samples10,11 that the urine PSA concentration is not dependent on serum PSA. Renal dysfunction also has no influence on the serum value.13,14 The measurable serum level in women varies between 0.0 and 0.2 ng/mL (the “female range”).15,16 Conversely, PSA secretion of the periurethral glands (potential “leak back”) also has no influence on the serum concentrations.17 The above-mentioned dilution effect was absent in our findings in female urine. Without exception, our analyses were carried out in first-stream urine, in which no clinically relevant dilution effect in urine samples up to a maximum micturition volume of 100 mL could be detected. The difference seems to depend on the known diverse morphologic findings in the male and female urethra. The emission of PSA by the periurethral glands during voiding appears to be different in men and women. Moreover, the average PSA level in the urine of men (median 10, 20, and 30 ng/mL18 median 300 ng/mL, range 6 to 442 ng/mL11) was found to be 30 to 1000 times higher than in the urine of women investigated in our department (0.29 ng/mL). Accordingly, in healthy men, the urinary PSA rates can be reduced to the female values by antiandrogenic therapy (untreated men median 10 to 30 ng/mL versus treated men 0.99 to 1.1 ng/mL, mean 0.251 ng/mL with cyproterone acetate).18 Likewise, androgen administration in women leads to increased urinary PSA levels (baseline level mean 0.017 ng/mL versus 18.130 ng/mL after testosterone treatment), so that the urinary PSA measurements may be useful as indicators of hyperandrogenism in women.19 Data on the age-dependent distribution of PSA concentration in women vary. On one hand, the female urethral glands remain rudimentary during the aging process (ie, they do not reach the histomorphologic change observed in men),1 correlating with the tendency toward lower urine PSA levels in older women compared with younger women. In accordance with our finding, Yu et al.20 found in an immunoreactive study of PSA tissue expression in breast tumors that PSA positivity declines with age, in conformity with a negative association between tissue PSA and age. The same observation was made by Melegos et al.21 in female serum of hirsute women. On the other hand, extraprostatic PSA production would appear to be under hormonal, androgen-dependent control.12,18–21 A corresponding study by Yu and Diamandis15 on female sera (n = 1064) revealed just the opposite tendency (ie, toward a PSA distribution pattern with higher levels in old age). Yu and Diamandis15 found that the menopausal status of these older women was responsible for the production of PSA. PSA production is known to be upregulated by androgen and suppressed by estrogen; after menopause, the ratio of estrogen to androgen declines, a situation that may favor PSA production.

The periurethral glands may be affected by urinary tract infections.22 Our study did not reveal a corresponding correlation in the form of a PSA level shift in urinary tract infections analogous to the frequent rise in serum PSA in prostatitis. Similarly, no evidence was found of a relation to residual urine status.

Graves et al.5 investigated the suitability of urine PSA in women relevant to the forensic aspects of sexual crimes. In addition to tissue-produced PSA, sexual intercourse is a possible cause of PSA in urine, because sperm contains high concentrations of PSA.5 Adult male volunteers were urine positive in this study and female volunteers were negative. The test used was not highly sensitive, having a less sensitive detection limit of 3.0 ng/mL.5 In contrast to the PSA levels measured in the urine after sexual intercourse in the studies of other investigators, some of them high,7–10 Graves et al., as well as ourselves, were unable to demonstrate an influence of sexual intercourse on PSA concentration or frequency in the urine of women. Of 7 women who had had sexual intercourse within 48 hours before sampling, only 3 had measurable positive PSA levels.

The question as to whether urine PSA might be an effective tumor marker has been investigated in many studies of men.6–10 Although De Vere White et al.7 found raised PSA levels more frequently in the midstream urine of prostatectomy patients than in serum and Tremblay et al.6 reported higher urine values than in healthy persons, the role of urine PSA as a screening parameter for tumors remains unclarified. PSA in the urine after prostatectomy could be caused by either residual prostate tissue or a local recurrence, or it could reflect the production of the urethral glands.7–10 In women, there are case reports of the rare adenocarcinoma of the female urethra originating in Skene’s glands,23 which is PSA positive according to Wernet et al.1 and others.24,25 Additionally, a case report of Skene’s gland adenocarcinoma showed an increased serum level of PSA preoperatively, which promptly decreased after surgical excision of the
lesion. Because of the rarity of this tumor, the presence of positive PSA in female urine on the basis of adenocarcinoma of the urethra would be very hard to prove.

**CONCLUSIONS**

In a unselected collective of urologic patients, 1 woman in 9 was positive for PSA in the urine. The finding seemed to be dependent on age and was without a dilution effect in small volumes. Influences arising from the factors pH, sexual intercourse, residual urine, and urinary tract infection were not evident.

**REFERENCES**


