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Relationship between Urinary Endogenous Steroid Metabolites and Lower Urinary Tract Function in Postmenopausal Women

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To investigate the relationship between the endogenous steroid hormones and the lower urinary tract function in postmenopausal women.

Thirty postmeopausal volunteer women who did not have lower urinary tract symptoms or hormone replacement therapy were enrolled in this study. Urodynamic studies included uroflowmetry, multi-channel cystometry, and urethral pressure profilometry were conducted. Gas Chromatography- Mass Spectroscopy(GC-MS) was used to measure the urinary endogenous steroid hormone metabolites. The relationship between the urinary profile of the endogenous steroids and the urodynamic parameters of these patients were investigated.

The mean ages of the patients were 60.6 ± 5.5 years, and the Body Mass Index (BMI) averaged 24.56 ± 2.23 (kg/m^2). Of the progesterone metabolites, pregnandiol was significantly related to the residual volume in the uroflowmetry and the functional urethral length parameters (R=0.98, p=0.000; R=-0.65, p=0.04). Pregnantriol was significantly related to the maximum flow rate, the residual volume in uroflowmetry, the maximum urethral closure pressure and the functional urethral length (R=-0.64, p=0.04; R=0.82, p=0.01; R=0.04, p=0.04; R=-0.79, p=0.01). In the androgen metabolites, androstenedione, 5-AT, 11- keto Et, 11-βhydroxy Et, THS, and THE were significantly related to the residual volume in uroflowmetry (R=0.92, p=0.001; R=0.84, p=0.008; R=0.99, p=0.000; R=0.72, p=0.03; R=0.97, p=0.000; R=0.85, p=0.00). β-THF/α-THF was significantly related to the maximum flow rate, the residual volume in uroflowmetry, the maximum urethral closure pressure and the functional urethral length (R=-0.76, p=0.02; R=0.67, p=0.04; R=0.74, p=0.02; R=-0.92, p=0.000). α-cortol was significantly related to the residual volume in uroflowmetry, the maximum urethral closure pressure and the functional urethral length (R=0.81, p=0.01; R=0.71, p=0.03; R=-0.87, p=0.000). Of the estrogen metabolites, estrone (E_1) was significantly related to the normal desire to void (R=0.68, p=0.04) and 17β-estradiol/estrone was also significantly related to the normal and strong desire to void (R=-0.70, p=0.03 and R=-0.74, p=0.02, respectively).

The urinary progesterone and androgen metabolite concentrations were positively related to the residual volume in uroflowmetry and positively or negatively related to MUCP and FUL. However, the urinary estrone concentration was positively related to the normal desire to void and 17β-estradiol/estrone was significantly related to the normal and strong desire to void.

Key Words: Steroid metabolites, menopause, urodynamic study

INTRODUCTION

The lower urinary and genital tracts are embryologically and anatomically closely related. Both are sensitive to the effects of female sex steroids, because the estrogen receptors are present in the vagina, urethra, bladder and the pelvic floor.[1-4] Symptomatic, cytological and physiological changes in the urogenital tract occur during the menstrual cycle, in pregnancy and in menopause.[5-9] Clinical studies have shown that both estrogen and progesterone might affect the incidence of certain lower urinary tract symptoms.[10-12] The incidence of many such symptoms has been shown to increase in approximately the fourth and fifth decades of life, which coincides with the

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time of menopause.[13] Some symptoms have also been shown to be either relieved or exacerbated by various forms of hormone replacement therapy.[14] In 1994, a meta-analysis showed that estrogen therapy results in a significant subjective improvement in the reported lower urinary tract symptoms. However, there was no objective improvement, as determined by a urodynamic test.[15] To date, no objective studies on the relationship between the endogenous steroid hormones including the estrogen and lower urinary tract function in postmenopausal women have been reported.

Therefore, the aim of this study was to determine the relationship between endogenous steroid hormones and a lower urinary tract function.

MATERIALS AND METHODS

From January 2000 to October 2000, 30 postmeopausal volunteer women who did not have lower urinary tract symptoms and were not undergoning hormone replacement therapy were enrolled in this study. All subjects were assessed by their standard history and a physical examination, as well as a urodynamic study. The urodynamic studies (Dantec-5000, Copenhagen, Denmark) included uroflowmetry, multi-channel cystometry, and urethral pressure profilometry. The urinary endogenous steroid hormone metabolite levels were measured by gas chromatography-mass spectrometry (GC-MS). This study investigated the relationship between the urinary profile of the endogenous steroids and the urodynamic parameters of the patients(maximum flow rate, average flow rate, total voided volume, residual volume, first desire to void, a normal desire to void, a strong desire to void, urgency, the maximal cystometric capacity, the maximum urethral closure pressure, the functional urethral length and their continence area). The Pearson correlation test was used for statistical analysis (SPSS software, SPSS INC, Chicago, Ill). A p value ≤ 0.05 was considered significant. Unless otherwise stated, all terminology used in this study conforms to the recommendations made by the International Continence Society.[16]

Materials

Androgen and estrogen standards were purchased from Sigma (St. Louis, Mo, USA). The d_2-17β-Estradiol used as an internal standard for the estrogen profile was purchased from MSD Isotope (Montreal, Canada). All solvents were of analytical grade and were used without additional purification. Serdolit AD-2 resin (particle size: 0.1 - 0.2 mm) was obtained from Serva (Heidelberg, Germany). β-glucuronidase/arylsulfatase from Helix Pomatia was acquired from Boeringer Mannheim (Germany). The (-glucuronidase activity was 5.5 U/ml (at 39℃) and the aryl sulfatase activity was 2.6 U/ml (at 38℃). Of the akylating reagent, MSHFB (N-methyl-N-trimethylsilyheptafluorobutyramide) was purchased from Machery-Nagel (Duren, Germany), and MSTFA (N-methyl-N-trimethylsilyltrifluoroacetamide), TMCS (trimethylsilylchloride), and TMSIm (N-trimethylsilylimidazole) were purchased from Sigma (St. Louis, MO, USA). Ethylacetate and ether were of a high purity "HPLC solvent" grade, and the ether was distilled prior to use.

Sample collection

Urine samples were obtained over a 24 hr period, and the first sample collection commenced at 10:00 a.m. The collected urine samples were stored at -20℃ until analyzed.

Gas chromatography-mass spectrometry

The Hewlett-Packard GC-MS system consisted of a gas chromatograph (HP 5972) and mass spectrometer (HP 5989B mass engine). The GC column used to separate the estrogens was a fused-silica capillary column coated with cross-linked 5% phenylmethyl siloxane (length: 25 m; inner diameter: 0.2 mm; film thickness: 0.33μm), while that used to separate the androgens and corticoids was a fused silica capillary column, which was coated with methyl siloxane (length; 17 m, inner diameter; 0.2 mm, film thickness: 0.11μm). Helium was used as the carrier gas (flow rate was 0.85 ml/min), and the split ratio was 1 : 10. The GC temperature program used is as follows: in the case of the estrogens, the initial temperature was 180

℃, which was increased to 260℃ at a rate of 20℃/min and held there for 6 min. Subsequently, the temperature was increased to 275℃ at a rate of 2℃/min and held for 8 min. Finally, it was further increased to 300℃ at a rate of 15℃/min and held for 10 min. For the androgens and corticoids analyses, the initial temperature (180℃) was programmed at 4℃/min to 300℃ and maintained for 2 min. The injector temperature was 300℃, the transfer line temperature was 300℃ and the temperture of the ion source was 200℃. The mass spectrometer was operated at 70 eV in electron-impact (EI) mode. A selected ion monitoring mode was used to quantify the 20 estrogens and 21 androgens. The dwell time for each ion was set at 50 msec.

Extraction of estrogens, androgens, and corticoids

A preconditioned Serdolit AD-2 resin was poured into a Pasteur pipette (inner diameter-0.5 cm) to 3 cm. The urine sample (3 ml) and the internal standard (d_2-17β-estradiol, 1.5μg for estrogens and methyl testosterone, 5μg for androgens and corticoids) were applied to the column. The free and conjugated endogenous steroids were eluted three times with 1 ml of methanol after washing the column with 3 ml of water. The combined eluent was evaporated to dryness using a rotary evaporator. Enzyme hydrolysis was performed using β-glucuronidase/arylsulfatase (from Helix Pomatia) with an acetate buffer (0.2 N, pH 5.0) at 55℃ for 3 hrs. Ascorbic acid(1 mg/ml) was added prior to hydrolysis of the estrogens in order to prevent the oxidation of catechol estrogens. Potassium carbonate was added after hydrolysis, and the pH was adjusted to 9.0. The mixture was extracted with 5 ml of ethyl acetate for the estrogens and 5 ml of ether for the androgens and corticoids. The organic layer was transferred to another tube and dried using a vacuum evaporator. The residue was then dried in a vacuum desiccator over P_2O_5/KOH to completely remove any moisture. The derivatization was performed by using a mixture of MSTFA and TMCS (100 : 1, volume ratio) at 60℃ for 30 min for the estrogens and MSHFB/TMCS/TMSIm (2 : 2: 1, volume ratio) at 60℃ for 10 min for both the androgens and corticoids. After cooling, 2μl of the aliquots were injected into the GC column using an auto sampler.

Assay

The concentration of following 20 estrogens: estrone [E1], 17β-estradiol [E2], 2-hydroxyestrone [2-OH E1], 2-hydroxyestradiol, 2-methoxyestrone [2-Meo E1], 17α-estradiol, 6-dehydroestrone, 6α-hydroxyestradiol, 4-methoxyestradiol, estriol [E3], 16-epiestriol [16-Epi E3], 16, 17-epiestriol, 16α-hydroxyestrone [16α-OH E1], 17-epiestriol, 6-ketoestriol, 2-methoxyestriol, 6-hydroxyestriol, and 16-ketoestradiol [16-Keto E2], as well as the following 21 androgens and corticoids: androgen [An], etiocholanolone [Et], dehydroepiandrosterone [DHEA], 4-androstenedione [$\triangle^4$-dione], testosterone [Te], 5-androstenediol [$\triangle^5$-diol], 11β-hydroxy An [11β-OH An], 11β-hydroxy Et [11β-OH Et], 16α-hydroxy DHEA [16α-OH DHEA], 5-androstene-3β, 16β, 17β-triol [$\triangle^5$-AT], tetrahydro-11-deoxycortisol [5α-THS], tetrahydrocortisone [THE], 5α-tetrahydrocortisol [5α-THF], 5α-tetrahydrocortisol [THF], α-cortolone, β-cortolone, cholesterol, α-cortol, β-cortol, 5β-tetrahydrocorticosterone [5α-THB] and 5β-tetrahydrocorticosterone [THB] were determined. All values were normalized to the urinary creatinine concentration.

RESULTS

The mean age of the subjects was 60.6 ± 5.5 years, and the Body Mass Index (BMI) averaged 24.56 ± 2.23 (kg/m^2). Of the progesterone metabolites, pregnandiol was significantly related to the residual volume measured by uroflowmetry as well as the functional urethral length (R=0.98, p=0.000; R=-0.65, p=0.04). Pregnantriol was significantly related to the maximum flow rate, the residual volume measured by uroflowmetry, the maximum urethral closure pressure and the functional urethral length (R=-0.64, p=0.04; R=0.82, p=0.01; R=0.04, p=0.04; R=-0.79, p=0.01) (Table 1).

Of the androgen metabolites, androstenedione, 5-AT, 11- keto Et, 11-β hydroxy Et, THS, and THE were significantly related to the residual volume

Table 1. Relationship Between the Concentrations (μmole/g creatinine) of Urinary Progesterone Metabolites and the Urodynamic Parameters

	Pregnandiol		Pregnantriol	
	R	*p*	R	*p*
Uroflowmetry				
Max.flow rate (ml/s)	-0.47	NS	-0.64	0.04
Aver.flow rate (ml/s)	-0.4	NS	-0.52	NS
Vol.voided (ml)	0.29	NS	0.05	NS
Residual urine (ml)	0.98	0	0.82	0.01
Filling Cystomety				
1st desire to void (ml)	0.14	NS	0.41	NS
Normal desire to void (ml)	-0.19	NS	0.09	NS
Strong desire to void (ml)	-0.43	NS	-0.23	NS
Urgency (ml)	-0.3	NS	-0.2	NS
Max.cystometric capacity (ml)	-0.19	NS	-0.14	NS
Urethral Pressure Profile				
Max.urethral closure pressure (cmH_2O)	0.38	NS	0.68	0.04
Functional urethral length (mm)	-0.65	0.04	-0.79	0.01
Continence area (mm $\times$ cmH_2O)	0.22	NS	0.39	NS

R, Regression coefficient; NS, Not significant.

measured uroflowmetry (R=0.92, p=0.001; R=0.84, p=0.008; R=0.99, p=0.000; R=0.72, p=0.03; R=0.97, p=0.000; R=0.85, p=0.00).

β-THF/ α-THF was significantly related to the maximum flow rate, the residual volume measured by uroflowmetry, the maximum urethral closure pressure and the functional urethral length (R=-0.76, p=0.02; R=0.67, p=0.04; R=0.74, p=0.02; R=-0.92, p=0.000). α-cortol was significantly related to the residual volume measured by uroflowmetry, the maximum urethral closure pressure and the functional urethral length (R=0.81, p=0.01; R=0.71, p=0.03; R=-0.87, p=0.000) (Table 2).

Of the estrogen metabolites, estrone (E_1) was significantly related to a normal desire to void (R=0.68, p=0.04) and 17β-estradiol/estrone was significantly related to a normal and strong desire to void (R=-0.70, p=0.03 and R=-0.74, p=0.02, respectively) (Table 3).

DISCUSSION

Progesterone receptors have been detected in the bladder wall and in the trigone[17,18] in women, and in the urethra and bladder of rabbits.[19] In dogs, progesterone has been found to increase the response of beta-receptors, which promote the relaxation of the smooth muscle sphincter.[20] In this study, the pregnandiol and pregnatriol levels were positively correlated to the residual urine volume, and pregnantriol was negatively correlated to the maximum flow rate. These results have been reported by othersp.[20] Rud, et al. found no change in the maximum urethral pressure profile with the use of agestagen, but did observe a decrease in the urethral pressure transmission during the cough profile.[21] However, in this study, FUL was negatively correlated with pregnandiol and pregnatriol but MUCP was positively correlated with pregnatriol. We are not sure of the

Table II. Relationship Between the Concentrations (μmole/g creatinine) of the Urinary Androgen Metabolites and Urodynamic Parameters

	Androsterone		5-AT		11-Keto Et		11β-Hydrxy An		11β-Hydrxy Et		THS		THA		THE		β-THF/α-THF		α-Cortol	
	R	P	R	P	R	P	R	P	R	P	R	P	R	P	R	P	R	P	R	P
Uroflowmetry																				
Max.flow rate (ml/s)	-0.47	NS	-0.33	NS	-0.42	NS	-0.41	NS	-0.19	NS	-0.44	NS	-0.07	NS	-0.49	NS	-0.76	0.02	-0.63	NS
Aver.flow rate (ml/s)	-0.39	NS	-0.34	NS	-0.35	NS	-0.41	NS	-0.25	NS	-0.4	NS	-0.15	NS	-0.41	NS	-0.64	NS	-0.52	NS
Vol.voided (ml)	0.22	NS	0.4	NS	0.35	NS	0.18	NS	0.29	NS	0.33	NS	0.12	NS	0.1	NS	-0.21	NS	0.01	NS
Residual urine (ml)	0.92	0.001	0.84	0.008	0.99	0	0.72	0.03	0.51	NS	0.97	0	-0.04	NS	0.85	0	0.67	0.04	0.81	0.01
Filling Cystometry																				
1st desire to void (ml)	0.10	NS	0.15	NS	0.02	NS	0.27	NS	0.26	NS	0.14	NS	0.3	NS	0.25	NS	0.57	NS	0.49	NS
Normal desire to void (ml)	-0.20	NS	0.05	NS	-0.29	NS	0.14	NS	0.34	NS	-0.15	NS	0.61	NS	-0.05	NS	0.14	NS	0.12	NS
Strong desire to void (ml)	-0.46	NS	-0.19	NS	-0.5	NS	-0.16	NS	0.09	NS	-0.4	NS	0.46	NS	-0.35	NS	-0.21	NS	-0.2	NS
Urgency (ml)	-0.41	NS	-0.17	NS	-0.38	NS	-0.21	NS	0.007	NS	-0.29	NS	0.23	NS	-0.33	NS	-0.17	NS	-0.12	NS
Max. cystometric capacity (ml)	-0.24	NS	-0.06	NS	-0.24	NS	-0.08	NS	0.009	NS	-0.17	NS	0.2	NS	-0.16	NS	-0.18	NS	-0.08	NS
Urethral Pressure Profile																				
Max.urethral closure pressure (cmH_2O)	-0.39	NS	0.48	NS	0.28	NS	0.6	NS	0.57	NS	0.41	NS	0.56	NS	0.52	NS	0.74	0.02	0.71	0.03
Functional Urethral length (mm)	-0.52	NS	-0.47	NS	-0.55	NS	-0.47	NS	-0.28	NS	-0.62	NS	-0.08	NS	-0.56	NS	-0.92	0	-0.87	0
Continence area (mm $\times$ cmH_2O)	-0.14	NS	0.48	NS	0.14	NS	0.44	NS	0.63	NS	0.29	NS	0.69	NS	0.21	NS	0.33	NS	0.4	NS

Table 3. Relationship Between the Concentrations (mole/g creatinine) of the Urinary Estrogen Metabolites and Urodynamic Parameters

	Estrone(E1)		17b-Estradiol(E2)		E2/E1	
	R	*p*	R	*p*	R	*p*
Uroflowmetry						
Max.flow rate (ml/s)	-0.02	NS	0.03	NS	-0.01	NS
Aver.flow rate (ml/s)	-0.06	NS	-0.18	NS	-0.25	NS
Vol.voided (ml)	-0.21	NS	-0.47	NS	-0.04	NS
Residual urine (ml)	-0.42	NS	-0.45	NS	0.55	NS
Filling Cystometry						
1st desire to void (ml)	0.38	NS	0.04	NS	-0.27	NS
Normal desire to void (ml)	0.68	0.04	0.17	NS	-0.7	0.03
Strong desire to void (ml)	0.55	NS	0.06	NS	-0.74	0.02
Urgency (ml)	0.3	NS	-0.18	NS	-0.52	NS
Max.custometric capacity (ml)	0.24	NS	-0.12	NS	-0.35	NS
Urethral Pressure Profile						
Max.urethral closure pressure (cmH_2O)	0.48	NS	0.08	NS	-0.32	NS
Functional urethral length (mm)	0.07	NS	0.38	NS	-0.08	NS
Continence area (mm × cmH_2O)	0.49	NS	-0.06	NS	-0.5	NS

R, Regression coefficient; NS, Not significant.

reason for these results, which differs from those reported in the literature.[21] In postmenopausal women, pregnantriol is the main progesterone[22] and pregnantriol has a closer relationship with both MUCP and FUL than with pregnandiol.

Rosenzweig, et al. found androgen receptors in the urethral and trigonal eipthelium of nonestrogenized rabbits in high concentrations, in the smooth muscle of the bladder and urethra in moderate concentrations and in the smooth muscle of the detrusor in low concentrations.[23] Kimura reported the presence of androgen receptors in the vesical smooth muscle of the human bladder.[24] Castrated female baboons, after testosterone treatments, exhibited an augmentation of their urethral pressure profile, which was similar to, but less profound than that following the estrogen treatment.[25] Iosif et al reported a modest decrease in both the urethral closure pressure and the pressure transmission ratio after danazol therapy.[26] In this study, the androgen metabolites were positively correlated with the residual urine volume. Androgen metabolites might be involved in the relaxation of bladder muscle in a similar to the progesterone metabolites. β-THF/α-THF was positively corrrelated with the MUCP and negatively correlated with FUL, which was similar to that reported in the literature.[25,26] In postmenopausal women, the main androgen is androsterone and many types of androgens could be produced by converting the enzymes that make them convertible with each other.[27]

The bladder and urethral function has become less efficient with age.[28] A previous study reported that elderly women have a reduced urinary flow rate, an increased urinary residual, a higher end-filling cystometric pressure, a reduced bladder capacity and a lower maximum voiding pressure.[29] The bladder neck and urethra contain the α-adrenoreceptors, the stimulation of which produces smooth muscle contractions and an increase in the urethral closure pressure.[30] Estro-

gen modifies the response of the urethra and bladder to α-adrenergic stimulation,[31] producing an increased sensitivity of the urethral smooth muscle. This is due to, at least in part, to an increase in the number of postjunctional α_2-adrenoreceptors.[32] In this study, estrone was positively correlated withthe bladder volume but 17β-estradiol was not significantly related to the bladder volume when there was a normal desire to void. The estrogenic potency of 17β-estradiol was stronger than that of estrone but the effect of the bladder storage function was higher under the influence of estrone than 17β-estradiol. Furthermore, 17β-estradiol/ estrone was negatively correlated with the bladder volume during the normal and strong desire to void, which is in contrast to previous reports.[29] In postmenopausal women, estrone (E_1) is the main estrogen, which is produced by a peripheral conversion.[33] Estrone exhibited a close relationship with the normal desire to void during filling cystometry, which might be explained by the fact that estrone was the main estrogen in postmenopausal women. This study is the first to investigate the relationship between the objective parameters of the bladder storage function and the urinary concentration of the estrogen metabolites. According to our data, estrogen does not greatly influence the storage function of the bladder. This study found that there was a minimal effect of the estrogen metabolites on MUCP and FUL. Estrogen is known to cause changes in the urethral mucosa, which might lead to an improved mucosal seal effect or hermetic closure. This coaptation of the urethra is believed to be largely due to the softness of the urethral epithelium.[34] In addition, the intrinsic urethral function may augment the action of estrogen caused by an increased periurethral vacularity.[35] Clinically, this study suggests that estrogen can be used to treat an overactive bladder because it is positively related to the storage function of the bladder. However, the results in this study showed that progesterone and androgen did not have any relationship with the storage function of the bladder and urethral function. Therefore, they have less potential as a potential drug for treating stress urinary incontinence and an over active bladder.

The steroid hormone metabolism depends on the steroidogenic enzymes[36] and the enzymic activity is a key step for the production of each hormone. Urinary assays continue to be of value in clinical practice because the changes in the estrogen metabolites in the urine may represent metabolic, rather than secretory changes.[37,38] The urinary steroid profiles have also been investigated for their utility as biochemical markers for diseases.[39-41] In order to overcome this limitation in measuring th serum estrogens in postmenopausal women, the urinary metabolite levels of estrogen were determined simultaneously using a sensitive GC-MS system. In this study,in order to enhance their specificity on gas chromatography, the sample preparation step was improved by extraxting the steroids with Serdolit AD-2 resin and deriving the steroids by trimethysilyation. The two main pathways of the estrogen metabolism are the 2-hydroxylation and 16α-hydroxylation pathways.[42] 2-hydroxylated estrogens have little estrogenic activity and in some experimental systems, they may even be antagonistic.[40]

Unfortunately, this study did not detect any 2-hydroxylated estrogens and 16α-hydroxylated estrogens. The levels of these hormones might be less than the detection limit. Therefore, the effects of the 2-hydroxylated estrogens on stress urinary incontinence could not be determined.

The estrogen metabolism may have genetic origins. The genetic factors affecting the enzyme activities are frequently important determinants of the disposition of drugs including exogenous and endogenous hormones as well as their efficacy and toxicity.[43] It has been proposed that racial patterns based on the gene polymorphisms of the cytochrome P450 enzyme are the reason for some of the differences observed in the estrogen metabolism between premenopausal Orientals and Caucasians.[44]

In conclusion, the urinary concentration of the progesterone and androgen metabolites positively correlated with the residual volume in uroflowmetry and positively or negatively correlated with MUCP and FUL. However, the urinary concentration of estrone positively correlated with the normal desire to void, and 17β-estradiol/estrone significantly correlated with a normal strong desire to void.

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