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Idiopathic Hyperestrogenism in Postmenopausal Women

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ABSTRACT. Idiopathic hyperestrogenism of unknown etiology in postmenopausal women (PIH), a new entity, was proposed. To clarify its etiology the 10 patients with this condition were observed. In 6 healthy postmenopausal volunteers who gave written consent, the adrenal and ovarian functions were investigated. Among the 10 PIH cases, a higher than normal serum level of estrone was observed in 4 cases and a level within the upper normal limit was noted in one case. The serum levels of estradiol and estriol, however, were normal in all cases. The increase of serum levels of estrone after ACTH load in the volunteers was seen in 3 cases, of serum estradiol in 5 cases (including 2 cases without ovaries due to previous surgical removal), of serum testosterone in 4 cases, and of serum Δ^4-androstenedione and dehydroepiandrosterone in all 6 cases.

These results suggest strongly that PIH is related to higher serum levels of estrone, which may be caused by an increased conversion rate of androgens to estrogens in the periphery and/or by an increased androgens production.

Stress was considered to be one of the factors to increase the conversion and/or production of androgens.

Key words : postmenopause — idiopathic hyperestrogenism

Idiopathic hyperestrogenism of unknown etiology in postmenopausal women has been reported by several authors. Novak *et al.*[1] and Brown *et al.*[2] found endometrial hyperplasias without pelvic pathologic condition in postmenopausal women. Limburg[3] observed elevated estrogen activity in the vaginal smears of 14.0% in women of aged 60 to 80 years old and Hustin *et al.*[4] reported 3 cases with positive cervical mucus ferning in more than 5 years after menopause. With the aim of studying the etiology of this condition, 10 cases were endocrinologically observed and the relationship of the condition to ovarian and adrenal functions was investigated.

SUBJECTS AND METHODS

The women passed more than 5 years after menopause without atrophy of the vestibulovaginal mucosa, and showed more than one of the following 3 signs were chosen : incidence of more than 20% superficial cells on maturation index of vaginal smear, positive cervical mucus ferning and endometrial hyperplasia. The patients with ovarian tumor, endocrine disorders or hormonal drug use were excluded. The 10 cases fulfilling these criteria were encountered in the author's outpatient clinic during the last 3 years. The vaginal smear maturation

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index test and an endometrial biopsy, if necessary due to uterine bleeding, were performed. Serum LH, FSH, estrone and estradiol in all cases and other steroids, including estriol, testosterone, Δ^4-androstenedione, progesterone, dehydroepiandrosterone, dehydroepiandrosterone sulfate and cortisol, and prolactin in some cases were determined by radioimmunoassays (RIA). Thirteen postmenopausal volunteers more than 5 years since menopause were used as a control group. The aims and methods of the study were explained in detail to all volunteers and their written consent was obtained. Of these thirteen volunteers, six underwent ACTH stimulation and dexamethasone suppression and hexestrol suppression tests. Tetracosactide acetate (®Cortrosyn) 0.25 mg was administered intravenously, dexamethasone 8 mg/day was given per os for 5 days and hexestrol diphosphate sodium 10 mg/day was administered orally for 2 days. Serum gonadotropins and steroids were determined before, 30 and 60 minutes after ACTH administration, 3 days after administration of dexamethasone and 2 days after that of hexestrol. The following serum hormones were measured by RIA : LH, FSH, estrone, estradiol, estriol, testosterone, Δ^4-androstenedione, progesterone, dehydroepiandrosterone, dehydroepiandrosterone sulfate and cortisol. The paired-t-test was used to determine significant differences of the hormone levels between the basal condition and after these tests.

RESULTS

The clinical and laboratory findings of the 10 PIH cases are shown in Table 1. The patients ranged in age from 46 to 87 with a mean of 66.8 years. One patient, 46 years of age, had undergone the bilateral oophorectomy at 41 years old. The elapsed years after menopause ranged from 5 to 35 years with a mean of 17.1 years. Positive cervical mucus ferning was noted in 6 cases. A vaginal smear estrogen effect was found in 8 cases and endometrial hyperplasia was observed in 3 out of 5 cases who received endometrial biopsies. Case 10 showed negative cervical mucus ferning in spite of vaginal smear estrogen effect.

On the other hand, cases 8 and 9 showed a negative vaginal smear estrogen effect despite positive cervical mucus ferning. The chief complaints consisted of uterine bleeding in 6 cases, nipple hypersensitivity in 2 cases and a sensation of vestibulum swelling in 2 cases. The levels of LH ranged from 5.1 mIU/ml to 203.5 mIU/ml with a mean of 86.2 mIU/ml, and those of FSH ranged from 3.0 mIU/ml to 221.0 mIU/ml with a mean of 87.0 mIU/ml. The levels of estrone ranged from 34.5 pg/ml to 192.3 pg/ml with a mean of 95.2 pg/ml, and those of estradiol ranged from 27.7 pg/ml to 11.3 pg/ml except for one case with <5.0 pg/ml, with a mean of 16.8 pg/ml. Those of estriol were <5.0 pg/ml in all 5 cases.

The levels of estrone and estradiol in the control group ($n=13$) were 41.2 ± 26.3 pg/ml (mean$\pm$SD) and 13.0 ± 10.0 pg/ml (mean$\pm$SD), respectively. The mean age of the control group was 64.6 and the average number of years after menopause was 18.2. The levels within the mean$\pm$2SD of serum estrone and estradiol in the control were employed as the normal levels in the postmenopausal women.

A higher level of estrone was noted in 4 PIH cases and a level near to the upper normal limit was observed in one case. The levels of estradiol and estriol were normal. The slightly higher levels of testosterone were found in all 5 cases

TABLE 1. Idiopathic hyperestrogenism in postmenopausal women

	Yrs. of age	Yrs. after menopause	Cervical mucus ferning	Vaginal smear maturation index	Endometrial biopsy	Chief complaints	LH (mIU/ml)	FSH (mIU/ml)
1 M.K.	60	7	(卄)	0/20/80	hyperplasia	uterine bleeding	100.0	43.5
2 K.W.	78	26	(卄)	13/65/22	atrophy	uterine bleeding	92.8	93.4
3 K.K.	75	25	(卄)	0/33/67		uterine bleeding nipples hypersensitivity	5.1	3.0
4 A.F.	58	9	(−)	5/63/32		vestibulum swelling	107.9	91.4
5 I.K.	65	17	(−)	0/42/58	hyperplasia	uterine bleeding	84.7	118.4
6 F.S.	87	35	(−)	0/47/53		vestibulum swelling	203.5	221.0
7 E.K.	46	5	(卄)	0/70/30		uterine bleeding nipples hypersensitivity	49.7	52.3
8 T.K.	58	6	(卄)	52/48/0			78.0	83.0
9 K.I.	71	25	(卄)	5/95/0	atrophy		95.0	92.9
10 S.T.	70	16	(−)	1/19/80	hyperplasia	uterine bleeding	45.0	71.0

	Estrone (pg/ml)	Estradiol (pg/ml)	Estriol (pg/ml)	Testosterone (ng/ml)	Androstenedione (ng/ml)	Progesterone (ng/ml)	Dehydroepiandrosterone (ng/ml)	Dehydroepiandrosterone sulfate (ng/ml)	Cortisol (μg/dl)	Prolactin (ng/ml)
1 M.K.	127.9	18.4	<5.0						35.0	6.4
2 K.W.	74.9	12.4	<5.0	1.0		0.6				
3 K.K.	116.2	15.8								7.6
4 A.F.	78.5	27.7								13.4
5 I.K.	59.4	15.6		0.7						20.0
6 F.S.	192.3	13.2	<5.0							11.5
7 E.K.	34.5	22.0								
8 T.K.	91.7	<5.0	<5.0	0.8	0.7	0.2	5.1	696.0	12.3	
9 K.I.	48.9	11.3		1.1	1.2					12.2
10 S.T.	128.0	14.8	<5.0	0.7	0.3	0.2	0.6	<200.0	5.4	23.0

normal : estrone 41.2±52.6 pg/ml (M±2SD), estradiol 13.0±20.0 pg/ml (M±2SD) in healthy postmenopausal women (average 18.2 years after menopause) (n=13)

〔control 0.23±0.40 ng/ml, mean±2SD, n=6〕. Dehydroepiandrosterone and dehydroepiandrosterone sulfate were slightly elevated in case 8. The degree of the obesity was judged by a modified Broca's method and calculated by the formula ; (body weight/ideal body weight)×100%, and ranged from 76.0% to 87.2% in 9

TABLE 2. Profiles of the volunteers for ACTH, dexamethasone and hexestrol tests

	Yrs. of age	Yrs. after menopause	Body length (cm)	Body weight (kg)	The degree of the obesity (modification by Broca (%))	Hyper-lipidemia	Remarks
1 M.H.	87	42	150.0	41.0	82.0	(−)	
2 S.K.	59	19	156.7	62.5	110.2 Slightly obese	(+)	
3 Y.K.	50	6	160.2	63.5	111.4 Slightly obese	(−)	bilateral oophorectomy at 44 yrs. old
4 K.M.	66	23	147.1	42.0	99.1	(−)	
5 T.K.	66	10	142.0	38.8	102.6	(−)	
6 F.M.	57	11	161.0	47.5	84.8	(−)	bilateral oophorectomy at 46 yrs. old

TABLE 3. Basal levels of gonadotropin and steroid before ACTH test in the volunteers

	LH (mIU/ml)	FSH (mIU/ml)	Estrone (pg/ml)	Estradiol (pg/ml)	Estriol (pg/ml)	Testosterone (ng/ml)
1 M.H.	68.0	70.0	26.1	<5.0	<5.0	0.3
2 S.K.	76.0	85.0	69.6	14.5	<5.0	<0.1
3 Y.K.	78.0	110.0	72.4	10.7	<5.0	<0.1
4 K.M.	110.0	110.0	66.2	6.5	<5.0	<0.1
5 T.K.	86.5	100.0	89.7	<5.0	<5.0	0.2
6 F.M.	84.0	84.0	49.8	11.3	<5.0	0.6

	Androstene-dione (ng/ml)	Progesterone (ng/ml)	Dehydroepi-androsterone (ng/ml)	Dehydroepi-androsterone sulfate (ng/ml)	Cortisol (μg/dl)
1 M.H.	1.8		0.2	234.	11.8
2 S.K.	0.1	0.2	1.1	269.	7.8
3 Y.K.	0.1	0.2	1.3	336.	7.7
4 K.M.	0.1	0.2	1.2	561.	3.9
5 T.K.	0.1	<0.2	<0.1	<200.	6.7
6 F.M.	0.9	0.2	3.2	358.	10.9

cases and was 119.0% only in case 10. Hyperlipidemia was observed only in case 2.

The profiles of the 6 volunteers are shown in Table 2. They ranged in age from 50 to 87 with a mean of 64.2 years and the number of years after menopause ranged from 6 to 42 with a mean of 18.5 years. Cases 3 and 6 underwent the total abdominal hysterectomy with bilateral salpingooophorectomy for ovarian benign neoplasms at the age of 44 and 46 respectively. Cases 2

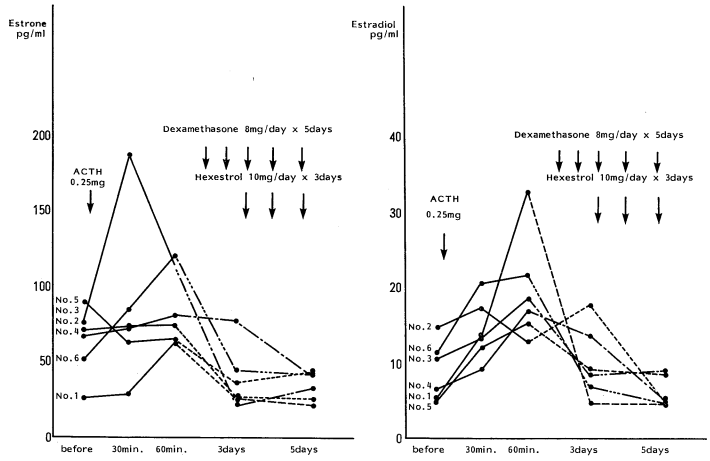

Fig. 1. Levels of estrone and estradiol in the volunteers in ACTH, dexamethasone and hexestrol tests

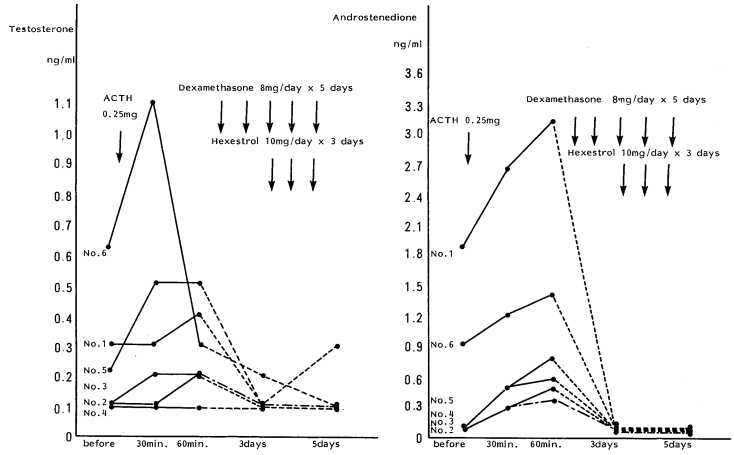

Fig. 2. Levels of testosterone and Δ^4-androstenedione in the volunteers in ACTH, dexamethasone and hexestrol tests

and 3 were showed slightly obese and other 4 cases were within normal. They were not including more than 20% overweight in this study. Hyperlipidemia was found only in case 2. The basal levels of gonadotropins and steroids are shown in Table 3. Changes in the levels of steroids after ACTH, dexamethasone and hexestrol are shown in Fig. 1 (estrone and estradiol), Fig. 2 (testosterone and Δ^4-androstenedione), Fig. 3 (progesterone and dehydroepiandrosterone), Fig. 4 (dehydroepiandrosterone sulfate and cortisol), and the average levels of the hormones of these 6 cases before and after the tests are shown in Table 4.

The higher serum levels in those at 30 or 60 minutes were compared with the basal levels. The increased ratio more than 1.5 times was dealt with a positive increase.

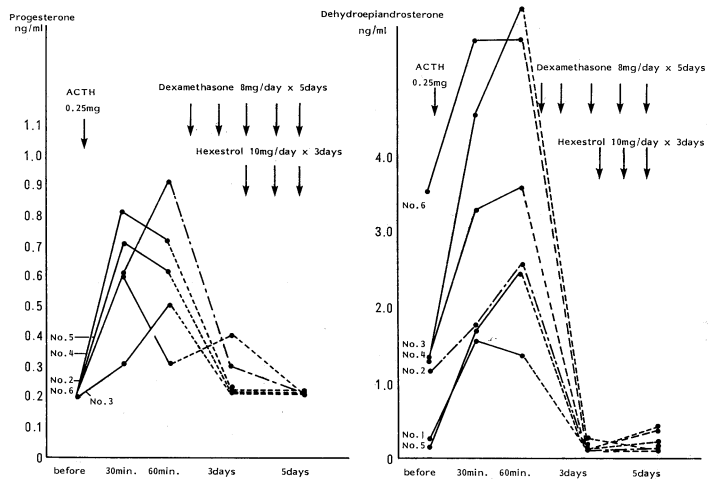

Fig. 3. Levels of progesterone and dehydroepiandrosterone in the volunteers in ACTH, dexamethasone and hexestrol tests

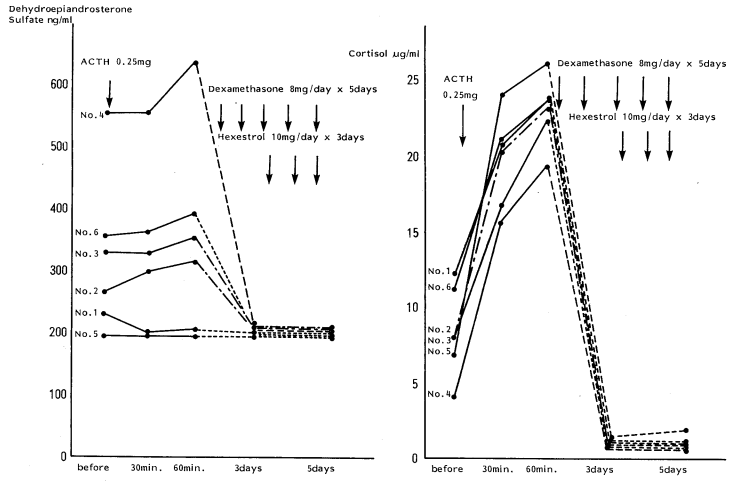

Fig. 4. Levels of dehydroepiandrosterone sulfate and cortisol in the volunteers in ACTH, dexamethasone and hexestrol tests

The increased ratios of estrone, ranged from 0.7 to 2.5 times after the ACTH load, and those of estradiol were from 1.2 to 6.5 times. A positive increase of estrone was seen in 3 cases (cases 1, 3 and 6), and that of estradiol was seen in 5 cases (cases 1, 3, 4, 5 and 6). The average levels of estrone increased at 30 and 60 minutes after ACTH, but not significant. The average levels of estradiol increased significantly at 30 and 60 minutes after the test ($p<0.05$ and $p<0.01$, respectively). The increased ratios of testosterone ranged from 0.5 to 2.5 times and the positive increase was noted in 4 cases (cases 2, 3, 5 and 6). The increased ratios of Δ^4-androstenedione ranged from 1.8 to 8.0 times and the positive increase was seen in all 6 cases. The average levels of testosterone after the test, however, did not differ significantly. The increased

TABLE 4. Average levels of steroids of volunteers before and after tests

	Basal	30 min. after ACTH	60 min. after ACTH	3rd day of dexamethasone	2nd day of dexamethasone and hexestrol
Estrone (pg/ml)	62.3±21.9	84.4±52.2	84.9±23.9	39.3±20.9	35.0± 8.4
Estradiol (pg/ml)	8.8± 3.9*	14.4±3.6*	19.6± 6.9⊗	10.5± 5.0	9.2, 8.8 others <5.0
Estriol (pg/ml)	< 5.0	< 5.0	< 5.0	< 5.0	< 5.0
Testosterone (ng/ml)	0.23±0.20	0.38±0.38	0.28±0.37	0.12±0.04	0.3 others <0.1
Androstenedione (ng/ml)	0.52±0.71	0.90±0.90	1.13±0.32	0.1, 0.1, 0.1 others <0.1	0.1 others <0.1
Progesterone (ng/ml)	≦0.20**	0.60±0.19**	0.60±0.22**	0.26±0.01	0.2, 0.2 others <0.2
Dehydroepi-androsterone (ng/ml)	1.18±1.12*	2.97±1.65	3.48±1.79*	0.12±0.04*	0.22±0.15
Dehydroepi-androsterone sulfate (ng/ml)	326±130*	332±135	355±162	<200*	<200*
Cortisol (μg/dl)	8.1±2.8***	19.5±3.1***	22.9±2.1***	1.1±0.5***	1.2±0.4***

values with statistic significant difference

*	p<0.05	(mean±SD)
⊗	p<0.01	compared with basal levels (paired-t-test)
**	p<0.005	
***	p<0.001	

n=6 [progesterone (n=5)]

ratios of progesterone and dehydroepiandrosterone ranged from 1.5 to 4.5 times, and from 1.3 to 8.0 times, respectively. This increase was seen in all cases. The average levels of progesterone and dehydroepiandrosterone increased significantly after ACTH stimulation ($p<0.005$ and $p<0.05$). The increased ratios of dehydroepiandrosterone sulfate ranged from 0.9 to 1.2 and increase was not seen. The average levels of cortisol increased significantly after the test ($p<0.001$).

With dexamethasone suppression, the estrone levels were ranged from 0.3 to 1.2 times in relation to the basal level. Three cases showed no suppression (cases 1, 4 and 6). The levels of estradiol were ranged from 0.6 to 2.1 times. Four cases were suppressed (cases 2, 3, 4 and 5). The levels of testosterone, Δ^4-androstenedione, dehydroepiandrosterone, dehydroepiandrosterone sulfate and cortisol were suppressed in all cases. The levels of progesterone were not suppressed in 5 cases.

With dexamethasone and hexestrol suppression, the levels of estrone before and after hexestrol administration changed from 0.5 to 1.5 times. Four cases were showed no suppression (cases 2, 3, 5 and 6). The levels of estradiol changed from <0.1 to 1.1 times. Two cases revealed no suppression (cases 3 and 5). The levels of testosterone, Δ^4-androstenedione and dehydroepiandrosterone were not suppressed in 2 cases (cases 4 and 5), but were suppressed in the other 4 cases

(cases 1, 2, 3 and 6). The levels of the remaining cases could not be evaluated because the assay was not sensitive enough to detect them. No suppression of progesterone was seen in one case (case 5). Serum levels of cortisol were not suppressed in 3 cases (cases 1, 5 and 6). The suppression of dehydroepiandrosterone sulfate could not be evaluated because the levels in all cases were under sensitivity of the assay.

DISCUSSION

In the 10 PIH cases a higher serum level of estrone than that of the control was seen in 4 cases and a level near to the upper normal level was noted in 1 case. A normal level of estradiol and a slightly higher level of testosterone were noted in all cases.

Based on the clinical findings of postmenopausal idiopathic hyperestrogenism, a higher level of serum estrone appears to be strongly related to its etiology. Several authors reported the existences of the cases with this peculiar condition, but there has been no discussion on its cause.

There appear to be three possible mechanisms involved in the higher levels of estrone in PIH, and in the increases in estrone and estradiol after ACTH test in the volunteer cases : 1) direct production of estrogens from the ovary, 2) direct production of estrogens from the adrenals, 3) estrogens production by conversion of androgens from the ovary and/or adrenal in the periphery.

In 6 volunteers, the levels of estrone which increased more than 1.5 times was seen in 3 cases (cases 1, 3 and 6), and serum levels of estradiol were increased more than 1.5 times in 5 cases (cases 1, 3, 4, 5 and 6) after ACTH load. Since the levels of estrone and estradiol were increased by ACTH in cases 3 and 6, who had on ovary, and the differences in serum levels of estrone and estradiol following dexamethasone and dexamethasone plus hexestrol were not significant, the postmenopausal ovary might not participate in direct production of estrogens. Longcope *et al.*[5] reported estradiol and testosterone production from the ovary in some cases of postmenopausal women. Vermeulen[6] and Judd *et al.*[7] on the other hand, described that the postmenopausal ovary could produce a very small amount of estrone, but no estradiol or progesterone. No significant difference has been noted between serum levels of estrone and estradiol in periphery and in postmenopausal ovarian veins taken by the catheter method[7,8] and the in vitro biosynthesis of estrogens could not be found with postmenopausal ovary.[6,7] It seems likely, therefore, that the main mechanisms involved in the serum levels of estrogens in postmenopausal women are not related to direct production of estrogens from the ovary.

The levels of estrone and estradiol were not suppressed by dexamethasone in 3 volunteers (cases 1, 3 and 6) and in 4 cases (cases 1, 2, 3 and 4). The differences in the average levels of estrone and estradiol before and during suppression were not significant. Enriori *et al.*[9] demonstrated that the normal adrenals cannot biosynthesize estradiol and Baired *et al.*[10] stated that the adrenal can produce estrone, but only up to 10% of normal serum levels at maximum. Therefore, the possibility of direct production of estrogens from the adrenal also appears unlikely.

The conversion of androgens to estrogens in the periphery thus seems to

be one of the mechanisms causing higher levels of estrone in PIH and the increases in estrogens in volunteers after ACTH test. Among PIH cases, there were 5 cases with the higher levels of testosterone than the control. The serum levels of dehydroepiandrosterone and dehydroepiandrosterone sulfate were higher in case 8. The levels of testosterone were increased by the ACTH test in 4 volunteers (cases 2, 3, 5 and 6), and of androstenedione and dehydroepiandrosterone increased in all 6 cases. These three androgens were suppressed by dexamethasone in all cases. Further suppression of the androgens by hexestrol plus dexamethasone was not seen in testosterone (case 5), in Δ^4-androstenedione (case 4) or in dehydroepiandrosterone (cases 1, 2, 5 and 6). The results suggest that three androgens originated mainly from adrenal in postmenopausal women, although the extent of the contribution of androgens from the ovary was unclear. Greenblatt *et al.*[11] stated testosterone production increased in the postmenopausal ovary and Jansen *et al.*[12] described Δ^4-androstenedione production decreased markedly in postmenopausal ovary as compared with the premenopausal ovary. Vermeulen[6] demonstrated serum testosterone was originated mainly in peripheral conversion of Δ^4-androstenedione from the adrenal and ovary. Both organs could produce only small amount of testosterone. On the peripheral aromatization of androgens, Grodin *et al.*[13] reported almost all serum estrone was derived from serum Δ^4-androstenedione and MacDonald *et al.*[14] noted that the conversion of testosterone to estradiol was markedly lower as compared with Δ^4-androstenedione. Longcope *et al.*[15,16] showed the transfer constant of estrone to estradiol to be 5% and that of testosterone to estradiol to be 0.15%. Siiteri *et al.*[17] demonstrated the injection of Δ^4-androstenedione into postmenopausal women produced that increases in estrone and sometimes in estradiol. Ackerman *et al.*[18] reported fibrovascular stromal cells could convert estrone to estradiol. Therefore, the Δ^4-androstenedione→estrone→estradiol process has been generally accepted as the main conversion pathway in the periphery. The factors involved in the increase in peripheral conversion of androgens to estrogens are generally considered to be : 1. obesity, 2. aging, 3. liver cirrhosis, 4. hyperthyroidism, 5. alcoholism, 6. diabetes mellitus. In addition, since the marked increases in serum levels of estrogens were confirmed by ACTH stimulation in healthy postmenopausal volunteers in the present study, stress might be one of factors.

The possible endocrinological mechanisms of the etiology of postmenopausal idiopathic hyperestrogenism were suggested to be related to the increased conversion rate of androgens to estrogens in the periphery and/or the increase of androgens production from the adrenal or ovary, but the detailed processes causing the increase in conversion rate and androgens production need further investigations.

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