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Androgen and SHBG serum concentrations in late post-menopause women

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Summary

Background: The purpose of our study was to evaluate androgen and SHBG concentration in the blood serum of late post-menopausal women.

Material/Methods: We examined women between 65 and 75 years of age and compared their results to those of a group of women in reproductive age. All the subjects, in addition to medical and gynecologic examinations, had determinations done of bound testosterone, free testosterone, androstenedione, dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulphate (DHEAS), sex hormone binding globulin (SHBG), and estradiol.

Results: The mean concentration of bound testosterone was found to be higher in postmenopausal women than in young women. The concentration of free testosterone did not vary, while the concentration of androstenedione was lower in the postmenopausal women, as were the DHEA and DHEAS concentrations. The mean SHBG concentration was higher in the postmenopausal women, and lower in obese postmenopausal women than in non-obese women. No differences were found in terms of the examined parameters between subjects with cardiovascular diseases and those without, or between smokers and non-smokers.

Conclusion: The extinction of ovary function and aging of a woman is related to secondary changes of androgen concentrations in blood serum. In late postmenopausal women, the SHBG concentration increases, which is related to the increase of total testosterone concentration in blood serum. Obesity affects the reduction of SHBG concentration in blood serum in postmenopausal women. Cardiovascular diseases and smoking have no significant effect on androgen concentration and SHBG changes in blood serum in postmenopausal women.

key words: **aging • cardiovascular disease • obesity • sex hormone binding globulin (SHBG) • androstenedione • dehydroepiandrosterone (DHEA) • dehydroepiandrosterone sulphate (DHEAS) • estradiol**

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Table 1. Subgrouping of postmenopausal women on the basis of medical history and clinical examination.

BMI (kg/m²)			Cardiovascular diseases		Tobacco smoking >24 cigarettes/24 h	
<25	25–30	>30	Yes	No	Yes	No
N=16	N=10	N=9	N=18	N=17	N=9	N=26

Table 2. Comparison of BMI values and the parameters studied in the blood of postmenopausal women and women in reproductive age.

	Postmenopausal women	Women in reproductive age	Postmenopausal women	Women in reproductive age	Statistical significance
BMI kg/m²	22.51	20.77	4.66	2.30	None
Total testosterone concentration* nmol/l	2.17	1.05	0.66	0.49	$p<0.001$
Free testosterone concentration* pmol/l	3.88	3.22	2.32	2.60	$p<0.05$
Androstenedione concentration* nmol/l	3.70	7.40	2.34	3.14	$p<0.002$
DHEA concentration* nmol/l	6.70	29.15	5.82	20.24	$p<0.001$
DHEAS concentration* μmol/l	1.81	6.91	1.16	3.36	$p<0.001$
SHGB concentration* nmol/l	106.49	71.07	42.32	43.53	$p<0.002$
Estradiol concentration* pmol/l	15.63	249.41	19.92	304.61	$p<0.05$

BACKGROUND

The endocrinological and general changes in postmenopausal women result from both the extinction of the activity of the ovarian follicles and the general aging processes of tissues and organs. Both processes lead to disturbances of bodily functions, reducing the quality of life and potentially leading to diseases that can cause death or disability.

While the problems of estrogen deficiency in postmenopausal women have been well studied, further research is needed on the role of androgens and the changes in androgen concentrations in comparison with the premenopause period, as well as the consequences of these changes.

The objective of our research was to evaluate the changes in the serum concentrations of androgens and sex hormone binding globulin (SHBG) occurring in women several years after menopause.

MATERIAL AND METHODS

The study included 62 women, divided into two groups: the study group, comprised of 35 women in late menopause, and a control group consisting of 27 young women in reproductive age. 300 women aged 65–75 were selected from a list of residents of Katowice, according to a valid randomization procedure and generally accepted statistical criteria. In the same way, another 300 young women aged 19–40 were selected and invited to enroll in the study.

The inclusion criteria were age, computer-aided selection of the individual, and consent to participate in the study. The exclusion criteria were as follows;

- clinical signs of hyperandrogenism,
- endocrinopathy,
- cirrosis and insufficiency of the liver,
- thyroid diseases,
- cancer,
- diabetes,
- use of hormone-based drugs,
- ovariectomy,
- menstruation and reproduction disorders in young women.

All subjects had been residents of Katowice for at least 5 years.

For the purposes of further analysis the women in the study group were additionally subdivided into groups based on the body mass index, the presence or absence of serious diseases of the cardiovascular system (myocardial infarction or coronary insufficiency within the previous five years), and tobacco smoking (Table 1).

The examinations were performed in the outpatient clinic in 1999–2000. Apart from detailed medical examinations, the women enrolled were tested for bound testosterone, free testosterone, androstenedione, dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulphate (DHEAS), sex hormone binding globulin (SHBG), and estradiol. Hormone concentrations were radioimmunologically determined, with the use of sets manufactured by the US based company DPC.

A total of 868 hormone determinations were performed. All tests were performed in the Department of Isotope Diagnostics at the Silesian University of Medicine in Katowice.

Approval to perform the study was obtained from the Bioethical Commission of the Silesian University of Medicine in Katowice.

Statistical analysis

The results were analyzed using 'Statistica' software on an IBM PC. The conformity of the measurable variables was checked with the Kolmogorov-Smirnov test. The differences between the mean values of the variables

Table 3. Parameters studied in the blood of postmenopausal women in terms of BMI.

	BMI <25 kg/m²	BMI 25–30 kg/m²	BMI >30 kg/m²	Statistical significance
Total testosterone concentration nmol/l	1.96 (S=0.70)	2.38 (S=0.49)	2.31 (S=0.77)	None
Free testosterone concentration pmol/l	3.26 (S=2.39)	4.09 (S=2.21)	4.75 (S=2.29)	None
Androstenedione concentration nmol/l	3.31 (S=2.37)	3.49 (S=1.36)	4.60 (S=3.07)	None
DHEA concentration nmol/l	7.17 (S=6.20)	6.27 (S=2.74)	7.18 (S=5.51)	None
DHEAS concentration μmol/l	1.70 (S=1.14)	1.76 (S=0.97)	2.03 (S=1.49)	None
SHGB concentration* nmol/l	124.63 (S=42.05)	104.20 (S=38.81)	76.78 (S=30.70)	p<0.05
Estradiol concentration pmol/l	14.71 (S=14.16)	8.29 (S=2.26)	25.32 (S=14.01)	None

Table 4. Parameters studied in the blood of postmenopausal women in relation to cardiovascular diseases and tobacco smoking.

	Cardiovascular diseases			Tobacco smoking >24 cigarettes/24h		
	Yes (N=18)	No (N=17)	Statistical significance	Yes (N=9)	No (N=26)	Statistical significance
Total testosterone nmol/l	2.03	2.31	None	1.96	2.21	None
Free testosterone pmol/l	3.15	4.65	None	3.15	4.13	None
Androstenedione nmol/l	3.24	4.19	None	2.72	4.04	None
DHEA nmol/l	5.37	8.53	None	4.61	7.70	None
DHEAS μmol/l	1.57	2.06	None	1.35	1.98	None
SHBG nmol/l	109.44	103.35	None	115.22	103.46	None
Estradiol pmol/l	9.47	22.13	None	13.94	20.55	None

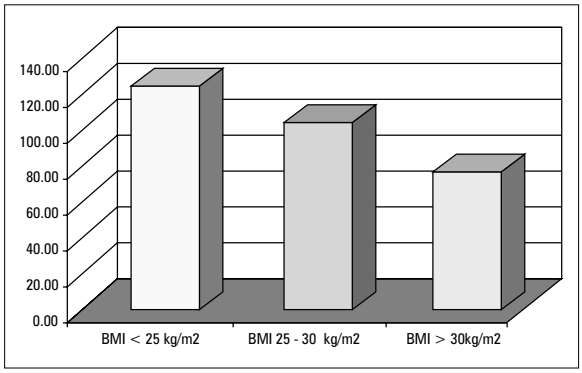

Figure 1. Mean SHBG concentration in postmenopausal women in relation to body mass index (BMI).

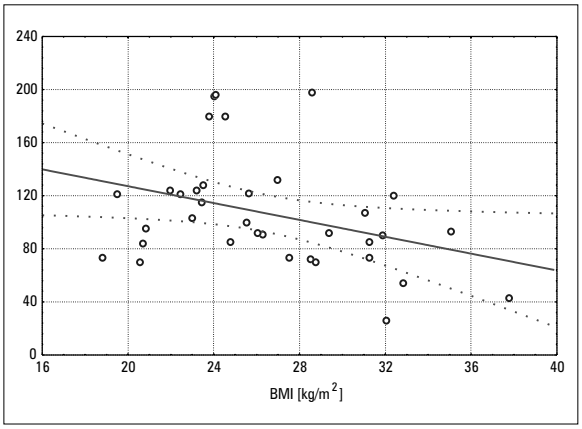

Figure 2. Correlation between BMI and SHGB serum concentration in postmenopausal women (r=-0.35, p<0.039).

were checked with the t-test, following the F-Fisher test to determine variance homogeneity.

RESULTS

The results obtained in the postmenopausal women as compared with those obtained from women in reproductive age are summarized in Table 2.

The bound testosterone and SHBG levels were found to be higher in the blood of postmenopausal women than in the control group, while the concentrations of androstenedione, DHEA, and DHEAS were lower. Free testosterone concentrations and BMI did not significantly differ between the groups.

The blood concentrations of the studied parameters in the postmenopausal women in relation to body mass index (BMI) are summarized in Table 3. The mean SHBG serum concentration was found to be lower in postmenopausal women with a BMI > 30 kg/m², in comparison to postmenopausal women with a BMI < 25 kg/m² (Figure 1). There is also a significant negative correlation between the BMI and SHBG serum concentration ($r = -0.35$, $p < 0.039$) (Figure 2). No significant BMI-related differences were found for the other parameters.

When the dependencies between the parameters studied in the postmenopause group and the incidence of cardiovascular diseases and tobacco smoking were studied, no significant correlations were found (Table 4).

When we examined the relations between estradiol concentrations and androgen concentrations in the serum of postmenopausal women, a significant correlation was

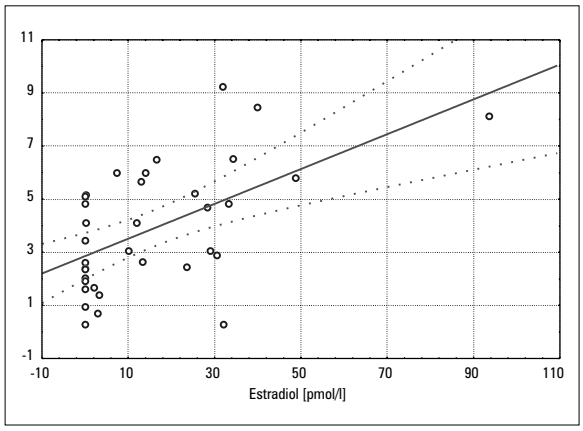

Figure 3. Correlation between estradiol and free testosterone of serum concentration in postmenopausal women (r=-0.56, p<0.001).

found for all the androgens studied: estradiol and androstenedione ($p< 0.015$; $r = 0.40$); estradiol and total testosterone ($p< 0.045$; $r = 0.40$); estradiol and DHEA ($p< 0.023$; $r = 0.38$); estradiol and DHEAS ($p< 0.014$; $r = 0.40$); the highest correlation was observed for estradiol and free testosterone ($r = 0.56$; $p<0.001$) (Figure 3).

DISCUSSION

It was demonstrated in the tests we performed that serum concentrations of androstenedione, DHEA, and DHEAS significantly decrease in late menopause when compared to women in reproductive age. Androstenedione is produced both in the ovary and in the adrenal glands, and the proportional share of either source changes with the time of day and the phases of the menstruation cycle [1,2]. Judd et al. [3] reported that after menopause the ovary is responsible for no more than 20% of daily androstendione production. In our study we found that mean androstenedione concentration in the serum of postmenopausal women is half that of young women. Similar results presented by Laughlin et al. [4] showed that the androstenedione level is about 10% lower in hysterectomized postmenopausal women with bilateral oophorectomy compared to those in intact women. The results obtained help to explain the theory that ovarian production of the hormone drops significantly with age, adrenal production drops slightly, and peripheral conversion to estrone increases. Thus it could be said that the postmenopausal period in women is linked with hypoandrostenedionemia, mainly due to extinction of the activity of the ovarian follicular structures.

Our study also found significantly lower mean DHEA and DHEAS concentrations in the serum of late postmenopausal women than in young women. These hormones are mainly produced by the adrenal glands, and only marginal amounts of DHEA originate from the ovaries (around 10%) [5]. DHEAS, on the other hand, is exclusively produced in the adrenal glands [6]. Both hormones are interconverted in the peripheral tissues to androstenedione, and later to testosterone and estrone [7].

The significant drop of adrenal secretion of androgens over the years, with a slight, though significant cortisol secretion, is related to reduced pulsed ACTH secretion. The cause for the drop in DHEA and DHEAS production include the changes in 17, 20 liase and 17 alpha hydroxylase activity in the reticular layer of the adrenal cortex, combined with a 30% reduction in the size of that layer, which occurs as a result of the aging of the body [8–10]. We may therefore say that the results of our study have confirmed the reduction of adrenal androgen production as a result of body aging. The age-related reduction of adrenal androgen production occurs in both sexes, although its consequences are probably different in women.

We found that free testosterone blood concentration was slightly lower in postmenopausal women than in young women, but the difference was not statistically significant. At the same time, the bound testosterone concentration increases by around 50% in older women, which is probably mainly due to a parallel increase in SHBG concentration. Laughlin et al. [4] have confirmed our observations. They demonstrated an increase in total, but not bioavailable testosterone levels with age, reaching premenopausal levels for ages 70–79, with relatively stable levels thereafter. In subjects between 50 and 89 years old, the range of androstenedione levels decreased about 27%, and SHBG levels increased about 30%. These authors also demonstrated that the foregoing changes were not present in oophorectomized women. An evaluation of these three parameters might suggest that ovarian testosterone production in postmenopausal women is not reduced, and the observed changes of concentrations of free and bound testosterone are a result of changes in SHBG concentration. Adashi [11] believes that the greatest quantity of serum testosterone in postmenopausal women originates from the ovaries. This has been confirmed by our results.

Moreover, a correlation was found in the postmenopausal women between estradiol concentration and androgen concentrations, which proves that these hormones are substrates for transformation into androgens.

These facts seem to have important clinical implications. If testosterone is a vital hormone in this period of a woman's life, if only by for its potential to convert into estrogens, then the preventive resection of non-diseased ovaries in postmenopausal women is not justified.

Our study also included an evaluation of the concentration of the protein responsible for the binding of SHBG. The concentration of this protein was found to be 44% higher in postmenopausal women than in younger women. Studies by Kwekkeboom et al. [12] have clearly proved that the age-related increase in the SHBG level occurs not only in men, but also in women. These results may seem surprising, as the postmenopause stage is linked with hypoestrogenism and, as demon-

strated in this paper, an unchanged testosterone secretion. Besides, insulin secretion and obesity increase with age in women, and so the SHBG-inhibiting factors increase [13]. It has been found, on the other hand, that IGF1 and SHBG concentrations are in inverse proportion to each other in both men and women [14,15], and from *in vitro* studies it is known that IGF1 inhibits the production of SHBG [16,17,18]. An age-related reduction of the inhibiting effect of IGF1 on SHBG synthesis may explain the observed increase of SHBG concentration in postmenopausal women.

Visceral obesity is observed more frequently in postmenopausal women than in other age groups. Among the women studied, 25% demonstrated obesity (BMI > 35). Unexpectedly, however, we did not observe any significant changes in the concentrations of the hormones studied among the obese women. Obesity was only significantly linked with serum SHBG concentrations. A statistically significant inverse correlation between BMI and serum SHBG concentration was also found. It should be noted, however, that these changes did not have any significant effect on the increase of free testosterone serum concentration.

In prospective studies, Barret-Connor et al. [19] found that the DHEAS concentration has an inverse correlation to the mortality rate in men above 50 years of age, irrespective of the causes of death, and to deaths caused by cardiovascular diseases. However, these interconnections do not occur in women. The above observations are in line with the results of our study. Nearly half the patients studied had either experienced myocardial infarction during the previous five years or had chronic ischemic heart disease. The concentrations of androgens, estradiol and SHBG in these persons did not significantly differ from the others. We confirmed that tobacco smoking does not influence the results of serum androgens and SHBG concentration.

In summary, we may say that the ovaries in postmenopausal women remain active endcorine glands. They produce significant quantities of androgens: testosterone and androstenedione. These hormones provide an important pool of substrates for extraglandular conversion of androgens to estrogens, and thus play an important role in the biological processes occurring in post-menopausal women. Laughlin et al. [4] argued that the postmenopausal ovary remain a critical source of androgen throughout the lifetime of older women. However, Couzinet et al. [20] published proof that the climacteric ovary is not a critical source of androgens. In their opinion, the adrenal contribution to circulating androgen levels plays an important role in the postmenopausal period of a woman's life. Continued research on androgen secretion and functions in postmenopausal women is very much needed.

CONCLUSIONS

1. The extinction of activity of the ovarian follicular structures and the aging of women is linked with secondary changes of serum androgen concentrations.
2. Women in late postmenopause demonstrate an increase in the blood concentration of SHBG, reduced by obesity.
3. Cardiovascular diseases and tobacco smoking have no significant effect on androgen and SHBG serum concentrations in postmenopausal women.

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