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Androgens and estrogens in relation to hot flushes during the menopausal transition

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Abstract

In this paper, the association of hormones to vasomotor complaints during the menopausal transition is discussed. Fifty-seven regularly menstruating women without history of hormone replacement therapy (HRT) were selected for a longitudinal, prospective study around the menopausal transition. The mean age at the start of the study was 51.3 ($\pm$2.0) years. At intervals of 12 months all women went through a semi-structured interview and filled in questionnaires. Venous blood samples were collected every 12-month for analyses of estradiol (E2), testosterone, androstendione, dehydroepiandrosterone-sulphate (DHEA-S), follicle stimulating hormone (FSH), thyrotropin (TSH), and luteinizing hormone (LH). Vasomotor complaints were tested using questions about hot flushes and bouts of sweating in terms of occurrence, frequency and degree of distress. Forty-six percent of the subjects reported hot flushes and bouts of sweating before menopause, increasing to 67% during the first year after menopause and 49% in the second year postmenopause. Low levels of estradiol and high levels of FSH were associated with vasomotor complaints before menopause. During menopause high levels of TSH were related to vasomotor complaints. The first year after menopause, women, who at this point achieved hot flushes, were characterised by high levels of E2, but declining and low levels of FSH, but increasing. Postmenopausal, high levels of testosterone and DHEA-S seemed to protect against vasomotor symptoms. Our most important finding was, that among women who achieved hot flushes at the first assessment postmenopause, the high androgen levels was a significant predictor of recovery from hot flushes at the last assessment, 1 year later.

Keywords: Menopause; Hot flushes; Estrogens; Androgens; TSH; Gonadotropins

1. Introduction

Vasomotor symptoms of 'hot flushes' and 'cold sweat' are the most common complaints in association with the climacteric period and are suffered by at least two-third of the climacteric women. The prevalence of these immediate symptoms differs in different studies [1–3].

The mechanisms responsible for hot flushes are not sufficiently known. The hot flush is essentially a vascular phenomenon. There is, however, no

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change in blood pressure during the period of altered peripheral blood flow and pulse rate. This makes it unlikely that a vasodilator causing widespread vasodilatation is released during hot flushes; if this were the case blood pressure would fall [4–6].

Hot flushes appear to originate within the central nervous system in the anterior hypothalamus and have been clearly linked to a transient lowered thermoregulatory set point, which activates the heat loss responses of sweating and increased peripheral blood flow [7].

Research on menopausal flushing so far has not provided a satisfactory explanation neither of its initiation nor of the episodic nature of the phenomenon.

The aim of the present study was to correlate vasomotor complaints to estrogens, androgens and gonadotropins longitudinally during the menopausal transition.

2. Methods

2.1. Subjects

The present study is part of the Norwegian Menopause Project (NMP), which is a prospective 5 years longitudinal study of the interaction between psychosocial and endocrine changes during the climacteric. The sample of women included in the study is based on a larger sample drawn from a population registry. Subjects were assessed with respect to data on hormone levels, vasomotor and other symptoms and psychological variables over a period of 5 years, following them through the menopausal transition. This design seemed useful for the purpose of studying the interactions between hormone values and other variables and their association to hot flushes. The original sample comprised 2349 individuals randomly selected from the population registry of the municipality of Oslo by the Central Bureau of Statistics of Norway. The inclusion criteria were that the participants should be female, Norwegian citizen, registered residents of the city of Oslo, and be 45–55 years of age. This large sample of women, participated in the cross-sectional part of the NMP. They were considered to be representative of the population, except that the level of general education, mean age at first pregnancy and number of abortions were slightly higher, and the number of births slightly lower than in the population in general [8].

From this original sample a representative sample, that is every fifth woman ($n = 200$) was drawn for a 5-year follow-up. Altogether, 193 (96.3%) of the women accepted the invitation to participate. One hundred and seventy-seven (91.7%) of these completed all parts of the study. Inclusion criteria for the final sample were:

1. The exact time point of the natural menopause could be determined.
2. Measurements were available on all relevant variables at all investigated time points.
3. No measurements at any time point were contaminated by artificial intervention, such as hormone replacement therapy (HRT) or low dose of estrogen, hysterectomy or oophorectomy.

In all, 120 (67.8%) of the women did not meet all the criteria for inclusion. Premenopausal measurements were lacking for seven (3.9%) of the women, due to the fact that they had already become postmenopausal at the start of the study (mean age 50.9 years S.D. $\pm$ 2.4 years) and one of them had also received HRT. Postmenopausal measurements were lacking for 43 (24.3%) of the women because they did not reach menopause during the course of the study (mean age = 49.5 years, S.D. $\pm$ 2.1 years). Postmenopausal measurements were also lacking for 52 (29.4%) of the women because of HRT (mean age = 52.0, S.D. $\pm$ 2.1 years). The postmenopausal measurements were disregarded in the case of 12 (6.8%) of the women who after 6-month period of amenorrhoea experienced one or more episodes of bleeding because of HRT. For two women the exact time point of menopause could not be decided because after 6 months of amenorrhoea they experienced further bleeding even though they did not receive HRT. Three (2.3%) of the women were hysterectomised (mean age = 48.5), one of whom also received HRT. Only one had a bilateral

oophorectomy. The final sample in the present study consisted of 57 regularly menstruating women, selected among these 177.

The mean age of the women at the start of the study was 51.3 years (S.D. $\pm$ 2.0, minimum = 47.3, maximum = 55.8). At enrolment all subjects were menstruating regularly. Mean age at menopause was 52.9 years (S.D. $\pm$ 2.1, minimum = 51.4, maximum = 59.7) with close to normal distribution.

2.2. Procedures

Blood samples, questionnaire and semi-structured interview data were collected once a year over a period of 5 years. In this paper, only hot flushes were related to the hormonal values.

In relation to the timing of menopause, data from all subjects were available, only at the last year before, and the first year after menopause. For this study data from three points in time are reported: (1) the last year before menopause (T1); (2) the first year subsequent to menopause (T2); and (3) the second year postmenopause (T3), where 39 of the 57 women were eligible for assessment. The remaining 18 women were less advanced in the menopausal transition, and accordingly were not included in the last assessment.

For practical reason the examinations were done at random in the menstrual cycle and the blood samples were taken between 10:00 and 15:00 h. The diurnal variation of follicle stimulating hormone (FSH), luteinizing hormone (LH), E2, and El are considered small, compared with the variation in the menstrual cycle. However, in order to relate the hormonal changes to the menstrual cycle, the serum progesterone was analysed before menopause. There was only one subject with luteal phase progesterone the last year before menopause.

There is some diurnal variation when considering dehydroepiandrosterone-sulphate (DHEA-S) and testosterone, and blood sampling at specific hour of the day may reduce high biological variations but the study design did not allow us to do so [9].

2.3. Measures

2.3.1. Vasomotor complaints

Three questions were designed to assess the occurrence of hot flushes and sweating during the menopausal transition. (a) Do you have hot flushes or bouts of excessive sweating? (b) How often would you say you suffer from hot flushes and bouts of sweating (ranging from one or two times a year to daily)? (c) When you have these hot flushes or bouts of sweating, would you say you are very troubled, moderately troubled or only slightly or not at all troubled by them?

The three variables that are constructed from these items are referred to as *occurrence*, *frequency*, and *distress*. Occurrence is a dichotomised variable (hot flushes or no hot flushes). Indexes were constructed for frequency and distress.

2.3.2. Hormone analyses

Hormones were determined in serum by different immunoassay techniques and are described in detail in a previous paper [10].

2.4. Statistical analyses

Analysis of variance (ANOVA) was applied to compare hormone levels of subjects with and without hot flushes. Post hoc analyses with Bonferroni correction were applied to compare subgroups of subjects.

The data for the hormonal levels showed a normal distribution after log transformation. SPSS version 8.0 for Windows was used for statistical analyses.

3. Results

3.1. Sample

Twenty-six (45.6%) of the subjects reported hot flushes and bouts of sweating before menopause, increasing to 38 (66.7%) in the first year after menopause. Among the 39 women who were eligible for assessment during the second year postmenopause, 19 (48.7%) reported hot flushes.

Among those who reported hot flushes and cold sweat, the frequency of the complaint varied considerably from daily to once or twice a year (Table 1).

At all three points in time, about one in five of the informants felt that their hot flushes and cold sweat represented a significant problem (Table 2).

3.2. Last year before menopause (T1)

At the last assessment before menopause (T1) women who reported hot flushes had significantly lower E2 levels and significantly higher FSH levels than individuals without flushes (Table 3). The low E2 levels and high FSH levels were most prominent in women who reported a high frequency of flushes. Among women who reported daily hot flushes no one had an E2 level above 0.07 nmol/l. Most women in this category also tended to have high FSH levels. The correlation between frequencies of hot flushes and hormone levels was significant for two hormones, i.e. E2 ($r = 0.34$, $P = 0.013$) and FSH ($r = 0.42$, $P = 0.002$).

3.3. First year postmenopause (T2)

From the last assessment before menopause (T1) to the first postmenopausal questionnaire (T2) an expected increase in the occurrence of hot flushes took place (Table 1).

Taken as a group, women with hot flushes had higher levels of TSH at T2, 2.07 IE/l (± 1.02) as compared with 1.31 IE/l (± 0.63; $P = 0.005$) among women without flushes.

Among the 31 individuals who did not report hot flushes before menopause, 15 women developed flushes in the first postmenopausal year (Fig. 1). Unexpectedly, this sub-group of 15 women (group E in Fig. 1) had significantly higher E2 levels and lower FSH levels before menopause than women who did not change in terms of hot flushes from pre to postmenopause (groups C and F; not shown in tables).

Among the 26 individuals who reported premenopausal hot flushes, as many as 23 women (88.5%) (group F in Fig. 1) still had flushes 1 year later. All the women who reported weekly or daily flushes premenopausal and tended to have low E2 and high FSH-values at T1, reported hot flushes also at T2 (and to the extent that data were available also at T3). They also tended to report more frequent flushes, also postmenopausally, than other sub-groups.

3.4. Second year postmenopause (T3)

Data from the second year postmenopause, (T3) were also available for 39 women. When women with and without hot flushes at T3 were compared, DHEA-S level at T2 was significantly higher ($P = 0.030$) and at T3 bordering to significance ($P = 0.054$) in women without hot flushes. A borderline significant trend was found for testosterone level measured both at T1 and T2 ($P = 0.079$, vs. $P = 0.054$). There was a trend that androstendione value at T1 and T2, but not at T3 was higher in women without hot flushes.

In order to evaluate the role of hormones in the changes of hot flushes from T1 through T2 to T3, three groups (Fig. 1) were compared. Group G;

Table 1
Occurrence and frequencies of hot flushes and bouts of sweating among women at three time points during the menopausal transition. Number of women, percentages in parentheses.

Frequency of symptoms	Last year before menopause (T1)	First year after menopause (T2)	Second year after menopause (T3)
Daily	11 (19%)	14 (25%)	8 (21%)
Weekly or less	5 (10%)	7 (12%)	8 (21%)
Monthly or less	10 (17%)	17 (30%)	3 (8%)
Never	31 (54%)	19 (33%)	20 (50%)
Total	57 (100%)	57 (100%)	39 (100%)

Table 2
Levels of distress among women with hot flushes and bouts of sweating the last year before menopause as well as the first and second year postmenopause

Distress	Before menopause (T1)	One year after menopause (T2)	Two years after menopause (T3)
Very troubled	7 (12%)	10 (18%)	7 (12%)
Moderately troubled	15 (26%)	29 (51%)	12 (21%)
Slightly or not troubled	35 (61%)	18 (31%)	20 (35%)
Total	57 (100%)	57 (100%)	39 (100%)

11 women who neither reported hot flushes at T1, T2 nor at T3. Group H; nine women who had hot flushes at T1, T2 or both, but who had recovered at T3, and finally group I; 19 women who still had hot flushes at T3. As many as 18 of the latter group had hot flushes both at T2 and T3 (ten of these even at T1). The group of women who at T3 had recovered from hot flushes (group H in Fig. 1) turned out to have significantly higher DHEA-S and testosterone levels both at T1 and T2 than the two other groups ($P = 0.001$, 0.005 and $P =$ 0.011, 0.005, respectively; Table 4). Androstendione had a borderline significance at T1 and T2 ($P = 0.046$ and 0.045, respectively; Fig. 2).

4. Discussion

A number of hormones have been considered important in explaining the symptoms of climacteric complaints. Hot flushes have been known to be effectively reduced or even relieved by treatment with estrogen replacement therapy. There is however, no acute change in estrogens levels before or during the flush itself. Hot flushes have been considered a consequence of the withdrawal of estrogens rather than the hypoestrogenism per se [11,12].

4.1. Hormones and hot flushes the last year before menopause (T1)

In our study, as has been seen in other studies [11,12] we found that low level of estrogens and high level of FSH was correlated to vasomotor complaints before menopause.

4.2. The first year postmenopause (T2)

In our assessment the first year postmenopause, as many as two thirds of the women reported hot flushes. Almost nine out of ten of the women who had flushes at T1 continued to have them at T2, and half of those who did not suffer from flushes at T1 acquired this complaint in course of the year up to T2. At this time hot flush is thus the statistically normal response to menopause. However, a number of the women reports relatively low frequencies of hot flushes. Even at T2 only 20% of the subjects report daily flushes.

At the time of menopause, the only hormone that was correlated to vasomotor symptoms, was TSH, which was positively associated with hot flushes. We have no good explanation of this phenomenon. Most authors have described a reduction in TSH level and subsequently a rise in T4 and T3 in postmenopausal women. Ballinger et al. [13] found that TSH was significantly elevated in the early postmenopausal group, among women who were clinically depressed, where FSH and LH were at maximum levels.

The hormonal profile of the women who were without flushes at T1 but had acquired them by T2 is unexpected. These women were characterised by high E2 levels and low FSH levels. All but two women without flushes at T1 who had E2 levels above 0.30 nmol/l (and correspondingly low FSH values) developed flushes at T2. Women with medium E2 levels (0.07–0.22 nmol/l) did not develop hot flushes. The women in group E, who got hot flushes at T2, tended to have very high E2 levels at T1, then displayed a marked drop in E2 levels at T2.

Table 3
Hormone levels (mean, S.D. in parenthesis) at assessment in the last year before menopause (T1) in women with and without hot flushes at that time

	FSH (IE/l)	LH (IE/l)	E2 (nmol/l)	Androstendione (nmol/l)	Testosterone (nmol/l)	DHEA-S (nmol/l)
Women without hot flushes at T1 ($n = 31$)	38.1 (26.7)	27.6 (14.3)	0.35 (0.41)	3.7 (1.5)	0.92 (0.54)	3.3 (1.8)
Women with hot flushes at T1 ($n = 26$)	56.9 (26.3)	33.0 (10.6)	0.16 (0.22)	2.9 (1.2)	0.74 (0.32)	3.50 (2.1)
Sign*	0.013*	0.127	0.041*	0.052*	0.150	0.636

The hormonal profile characterised by high E2, low FSH at T1 was shown to protect the women from vasomotor complaints before menopause.

Once menopause is reached, however, they seemed to be vulnerable to develop hot flushes associated with a marked drop in E2 levels. It should be noted, though, that these women (group E) tended to report less frequent flushes than those who reported flushes already at T1 (group F), and a third of them recovered from their flushes by the next assessment in the second year after menopause (T3; group H in Fig. 1).

4.3. The second year postmenopause (T3)

In the second year postmenopause, a role for the androgens seems to occur, as high androgen levels were significantly related to a recovery from hot flushes.

4.4. General discussion

The circulatory phenomena observed during the menopausal hot flush are not specific to the female. After orchidectomy [14] or the administration of GnRH agonist [15], men may also flush, and their symptoms can be as severe as those seen in menopausal women. It is indeed surprising that to our knowledge, no theory proposed thus far to explain the mechanism of hot flushes has taken into account the fact that men may also flush. Whilst one might speculate that the mechanism of flushing in men differs from that in women, that they in other words may flush for different reasons, it is more likely that the male after orchidectomy and woman after ovarian failure flush for the same reason. Androgens per se, independent of conversion to estrogens, suppress hot flushes because the use of fluoxymesterone, a non-aromatisable androgen was as active as methyltestos-

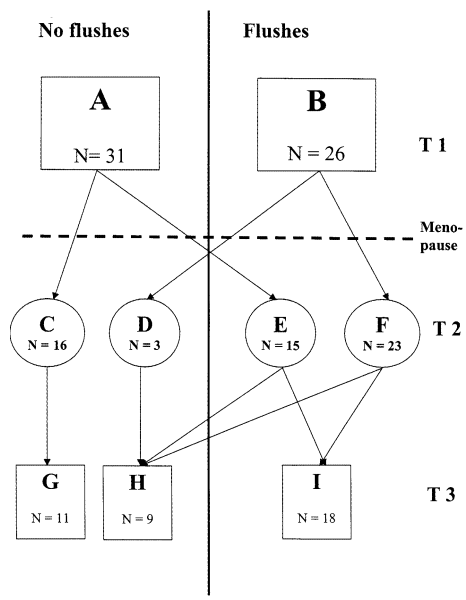

Fig. 1. At T1 (before menopause) 31 women (A) reported no hot flushes and 26 (B) reported hot flushes. At T2 (after menopause) 16 women of the 31 still did not report hot flushes (C), while 15 developed hot flushes (E). Of the 26 women who reported hot flushes at T1, only 3 recovered from hot flushes at T2 (D). One of these women reported hot flushes again at T3 (this is not shown in figure). At T3 (2 years postmenopausal) there were 11 women in the 'no flushes group' who still did not report hot flushes (G), while among the 38 women (E and F) with hot flushes at T2, nine (H) recovered from hot flushes at T3, and 19 still reported hot flushes (I). The arrow is omitted for one individual without hot flushes at T2 who got hot flushes at T3 (note, we do not have information from more than 39 women at T3).

Table 4
Androgen levels (mean and S.D.) during the menopausal transition, at 1 year before menopause (T1), 1 year after menopause (T2) and 2 years after menopause (T3), related to three different groups (group G, H and I)

Group	Last year before menopause (T1)	First year after menopause (T2)	Second year after menopause (T3)
Testosterone			
G (no flushes)	0.84 ($\pm$0.43)	0.71 ($\pm$0.30)	0.65 ($\pm$0.39)
H (recovery)	1.27 ($\pm$0.46)*	1.04 ($\pm$0.30)	0.94 ($\pm$0.35)
I (persistent)	0.77 ($\pm$0.40)*	0.67 ($\pm$0.30)	0.85 ($\pm$0.36)
Androstendione			
G (no flushes)	3.43 ($\pm$1.34)	2.97 ($\pm$0.99)	2.86 ($\pm$1.14)
H (recovery)	4.74 ($\pm$1.51)	3.82 ($\pm$1.58)	2.9 ($\pm$1.07)
I (persistent)	3.30 ($\pm$1.58)	2.75 ($\pm$1.08)	2.65 ($\pm$0.88)
DHEA-S			
G (no flushes)	3.16 ($\pm$1.45)*	3.45 ($\pm$1.58)	3.03 ($\pm$1.55)
H (recovery)	5.37 ($\pm$2.14)*	5.09 ($\pm$2.47)	3.98 ($\pm$1.79)
I (persistent)	3.00 ($\pm$1.58)**	2.99 ($\pm$1.21)	2.6 ($\pm$1.06)

*$P = 0.03$; **$P = 0.003$.

terone in relieving symptoms in a man with testosterone insufficiency [15]. If it is so, then the initiator may be neither estrogen nor androgen, but a substance common in both gonads and in whose absence, the activity of the thermoregulatory centre is disturbed.

Even though TSH values were significantly higher among women with hot flushes, we have not found that this tendency has any clinical relevance.

Androgens are natural components of ovarian secretion. They are important components of female health before and after menopause [16].

The menopause is also associated with a decrease in the overall testosterone production [17]. However, ovarian secretion of testosterone is maintained at a level approaching that in younger women, although the marked fall in secretion of androstendione, a major precursor of testosterone, results in an overall decline in circulating testosterone levels which is compounded by a decrease in non-ovarian production of testosterone. Thus the postmenopausal ovary remains an important source of testosterone production, and the decline in total circulating androgens with age results from a combination of ovarian failure and decreasing adrenal and peripheral androgen synthesis [17]. A recent study by Burger et al. did show that the levels of total serum testosterone were unchanged across the menopausal transition [18].

With the decrease in ovarian function at the menopause, peripheral aromatization of androgens becomes the major source of estrogens in postmenopausal women. It should be recalled that adrenal androgens contribute 95% of estrogenic activity in women (and they are also responsible for $>50\%$ of androgenic activity in women).

The age-related change in adrenal androgens is associated with considerable changes in intraadrenal enzyme activity, but without any concomitant changes in cortisol levels. DHEA-S, being strongly bound to serum albumin, shows very stable serum levels with very little, if any diurnal variation, in contrast to androstendione and DHEA [19,20]. In the present study we have demonstrated that high levels of DHEA-S protect against vasomotor complaints after menopause, together with testosterone and androstendione, these values were only close to significance.

In both sexes DHEA is almost exclusively and DHEA-S exclusively of adrenal origin and the levels of both these steroids decreases continuously with increasing age.

DHEA and its sulphated conjugate (DHEA-S) have recently attracted much attention because of the unusually dramatic (3-fold) decrease that is greater than any steroid change during middle age

in the human male; similar changes occur in women. It is estimated that 30–50% of total androgen formation in men are synthesised in peripheral intracrine tissues from inactive adrenal precursor [21–23].

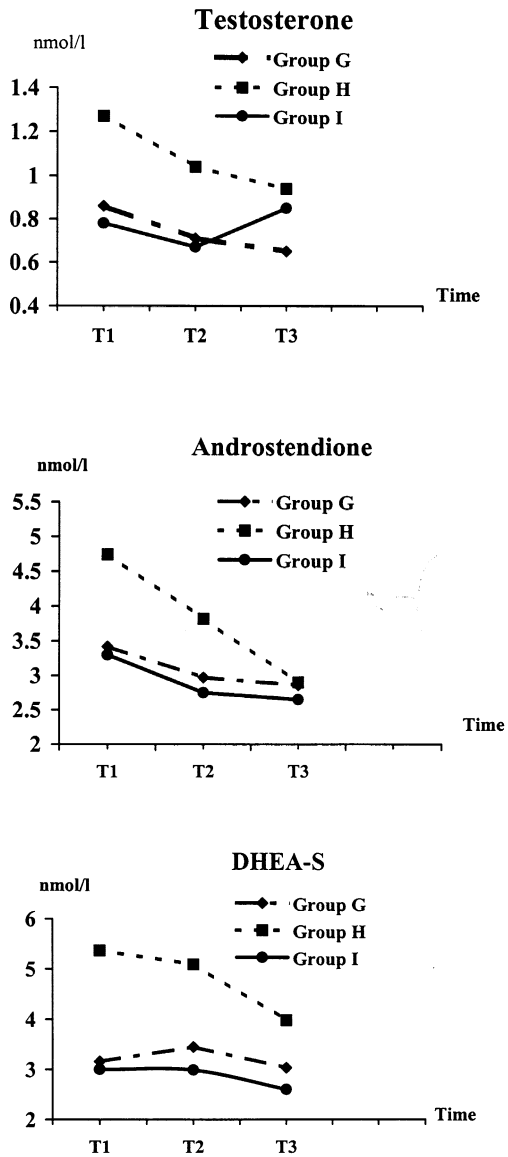

Fig. 2. Androgen levels related to three different groups (G, H, I) the second year after menopause. Group G consisted of 11 women who never had hot flushes. Group H consisted of nine women who recovered from hot flushes. And group I consisted of 18 women with persistent hot flushes.

Our study supports previous findings that androgens per se protects against vasomotor symptoms [13], especially after the menopause. Among those women who did not have hot flushes during the menopausal transition (T1–T3), the androgen levels tended to be close to the total sample mean. However, among those women, who at one point during the menopausal transition (T1–T2) had hot flushes, the androgen levels was a significant predictor of recovery from hot flushes.

Peripheral aromatization of androgens becomes the major source of estrogens in postmenopausal women, and that explains why FSH and LH are relatively low and E2 relatively high among women who recovers from hot flushes after menopause.

It should be noted that in this paper we have only related hot flushes to hormones. Other variables may contribute to the presence of hot flushes, and further research on this subject is needed.

In conclusion, it was possible to identify three different patterns among the hormonal changes observed during the menopausal transition in relation to vasomotor complaints. There were, firstly, a relationship premenopausally between hot flushes and low estrogen level and high FSH. Secondly, immediately postmenopausal there was a correlation of TSH to vasomotor symptoms. There was also a correlation between declining estrogens and vasomotor symptoms in a subgroup of women. Our most important finding was, that among women who achieved hot flushes at first assessment postmenopause, the high androgen levels was a significant predictor of recovery from hot flushes at the last assessment one year later.

Moreover, there was a negative correlation between androgens and vasomotor complaints also among women who did not acquire hot flushes at all.

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