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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Hot flash values of gonadotropins and estradiol in menopause

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SUMMARY

Introduction/Objective Hot flashes are one of the first clinical symptoms of menopause. The mechanism of hot flashes is still not fully understood. Changes in concentrations of the circulating follicle-stimulating hormone (FSH), luteinizing hormone (LH), estrogen, and other hormones can lead to thermoregulatory dysfunction.

The aim of this study was to examine the association between dynamic changes in concentrations of sex hormones and the presence of vasomotor symptoms in menopausal women.

Methods The study involved 36 women divided into two groups: in the first group there were 24 women with hot flashes, BMI 26.16 ± 3.42 kg/m^2; the control group comprised 12 women, BMI 26.82 ± 3.89 kg/m^2. Data on the presence of hot flashes were based on medical history data. Venous blood samples were collected for the analyses of FSH, LH, prolactin, estradiol, progesterone, testosterone, sex hormone binding globulin, dehidroepiandrosteron sulfate, thyroid-stimulating hormone, and thyroxin. During the subjective feeling of hot flashes, three blood samples during the day and night were collected to determine the mean levels of FSH, LH, and estradiol in women with hot flashes.

Results Women with hot flashes had significantly higher prolactin (389.58 ± 123.69 mIU/L to 258.19 ± 122 mIU/L, $p < 0.01$) and dehydroepiandrosterone sulfate (3.60 ± 2.49 nmol/L vs. 1.88 ± 1.27 nmol/L, $p < 0.05$) levels, as well as lower mean values of FSH during hot flashes during the day (69.08 ± 28.84 IU/L vs. 107.18 ± 39.11 IU/L, $p < 0.01$) and night (60.72 ± 21.89 IU/L vs. 104.57 ± 38.06 IU/L, $p < 0.01$).

Conclusion Women with hot flashes had significantly lower mean FSH levels during hot flashes during the day and night than the control group.

Keywords: hot flashes; menopause; sex hormones

INTRODUCTION

Hot flashes are one of the first clinical symptoms of menopause, causing considerable distress and reducing the quality of life of women [1]. They occur in climacterium in four out of 10 women over the age of 40 years. A recent review of the worldwide medical literature reported that the mean prevalence of vasomotor symptoms among women aged 40–64 years was 57% [2]; about 20% of women described them as unbearable [3].

Hot flashes are characterized by the sudden appearance of redness of the face and trunk, a sense of unbearable heat, excessive and rapid sweating. Feeling of the heat wave usually starts from the chest and spreads to the neck and face. It is accompanied, sometimes, by chills and profuse sweating, as well as reducing superficial skin temperature by 0.2°C. In most women, hot flashes are associated with sleep disturbances, anxiety, tension, depression, lack of concentration, and reduced sexual desire, which leads to the overall decrease of the quality of life.

The mechanism of hot flashes is still not fully understood. Since the central temperature is normal before the occurrence of hot flashes, it appears that hot flash starts with a reduction in the sensitivity of the central thermostat in the hypothalamus, leading to the activation of mechanisms for heat dissipation and changes in the functioning of the autonomic nervous system. The results of these changes are the vasodilatation of the skin blood vessels, redness, and sweating. A number of factors can lead to thermoregulatory dysfunction, such as changes in concentrations of estradiol (E_2), follicle-stimulating hormone (FSH), luteinizing hormone (LH), serotonin, norepinephrine, calcitonin gene-binding protein, and neuropeptide Y [4, 5, 6].

The aim of this study was to determine the association between the concentrations of sex hormones and the presence of vasomotor symptoms in menopausal women, as well as forming a group of women with hot flashes and high risk for cardiovascular diseases with the main purpose of preventing cardiovascular diseases.

METHODS

This study involved 36 women hospitalized in the Clinic for Endocrinology, Diabetes and

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Metabolic Diseases, Clinical Center of Serbia. The study group comprised 24 women with hot flashes, with the average age of 51.83 ± 4.48 years, with the body mass index (BMI) of 26.16 ± 3.42 kg/m^2. In the control group there were 12 women without hot flashes, with the average age of 57.17 ± 2.66 years and the BMI of 26.82 ± 3.89 kg/m^2. The presence of menopause was determined on the absence of menstrual cycles during the period of one year, estradiol levels lower than 50 pmol/L, and FSH levels higher than 40 IU/L. Data on the presence of hot flashes were based on medical history data. The women had no hypertension. Other diseases were excluded.

The following anthropometric parameters were measured in the patients: body height, body mass, and BMI. Venous blood samples were collected for the analyses of the FSH, LH, prolactin, estradiol, progesterone, testosterone, sex hormone-binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEAS), thyroid-stimulating hormone (TSH), and thyroxine (T4). Three blood samples during the day and night were taken from patients with hot flashes during the subjective feeling of hot flashes. Since hot flashes occur more than three times a day, it was necessary to take blood samples for hormone analyses at the moment of the hot flash occurrence. The time of sampling was defined by individual occurrence of hot flashes in menopausal women.

Plasma FSH (ImmuChem FSH-CT IRMA kit, ICN Biomedicals, Inc., Santa Ana, CA, USA; CV 2.6%), LH (ImmuChem hLH IRMA kit, ICN Biomedicals, Inc.; CV 2.4%), prolactin (ImmuChem kit, ICN Pharmaceuticals INC, Canada; CV 7%), estradiol (ESTR-US-CT Cisbio, Bioassays, Codolet, France; CV 2.8%), progesterone (PROG-CTRIA kit, CIS Bio International, Gif-sur-Yvette, France; CV 3.5%), testosterone (TESTO-CT2, Cisbio International; CV 3.1%), SHBG (SHBG-RIACT, Cisbio International; CV 3.6%), DHEAS (ImmuChem^{TM} kit, ICN Biomedicals INC, Irvine, CA, USA; CV 8.9%), TSH (IRMA hTSH kit, INEP, Belgrade, Serbia; CV 2.1%), T4 (RIA T4 kit, INEP, Belgrade, Serbia; CV 7.5%) were measured by a radioimmunoassay.

Statistical analyses were conducted using the SPSS for Windows, Version 16.0 (SPSS Inc., Chicago, IL, USA), having established that the data have normal distribution. A difference was considered statistically significant when the significance level was $p < 0.05$, and highly significant when the significance level was $p < 0.01$.

Informed consent was obtained from all the patients. The study was approved by the Ethics Committee of the Clinical Center of Serbia.

RESULTS

The mean age for the group with hot flashes was 51.83 ± 4.48 years vs. 57.17 ± 2.66 years for the control group. There was no statistically significant difference in the BMI and the age of menopause between the two groups of women.

The women with hot flashes had significantly more hot flashes during the day compared to night (6.75 to 4.5, $p < 0.01$). They also had significantly higher prolactin (389.58 ± 123.69 mIU/L vs. 258.19 ± 122 mIU/L, $p < 0.01$) and DHEAS (3.60 ± 2.49 nmol/L vs. 1.88 ± 1.27 nmol/L, $p < 0.05$) levels than the women in the control group. There were no significant differences in concentrations of FSH, LH, estradiol, testosterone, SHBG, T4, and TSH between the two groups (Table 1).

Table 1. Baseline hormonal levels in women with and without hot flashes

Hormones	Women with hot flashes	Women without hot flashes	p
FSH (IU/L)	64.80 ± 16.44	68.00 ± 33.41	0.70
LH (IU/L)	31.73 ± 12.79	30.54 ± 14.15	0.80
Prolactin (mIU/L)	389.58 ± 123.69	258.19 ± 122.00	0.01
Estradiol (pmol/L)	31.68 ± 14.52	33.24 ± 9.76	0.74
Progesterone (nmol/L)	4.44 ± 2.35	2.05 ± 1.57	0.01
Testosteron (nmol/L)	1.28 ± 0.71	1.15 ± 0.55	0.58
DHEAS (nmol/L)	3.60 ± 2.49	1.88 ± 1.27	0.03
SHBG (nmol/L)	56.13 ± 37.78	73.96 ± 38.64	0.19
T4 (nmol/L)	110.13 ± 12.09	104.25 ± 6.42	0.20
TSH (mIU/L)	2.02 ± 1.64	1.10 ± 0.63	0.08

FSH – follicle-stimulating hormone; LH – luteinizing hormone; DHEAS – dehydroepiandrosterone sulfate; SHBG – sex hormone-binding globulin; T4 – thyroxin; TSH – thyroid-stimulating hormone

Table 2. Mean values of sex hormones during the day and night episodes of hot flashes

Mean values	Women with hot flashes	Women without hot flashes	p
FSH day (IU/L)	69.08 ± 28.84	107.18 ± 39.11	0.01
FSH night (IU/L)	60.72 ± 21.89	104.57 ± 38.06	0.01
LH day (IU/L)	28.70 ± 16.35	32.91 ± 13.06	0.44
LH night (IU/L)	26.33 ± 11.87	32.44 ± 11.75	0.15
E_2 day (pmol/L)	28.17 ± 10,06	30.63 ± 13.56	0.54
E_2 night (pmol/L)	24.69 ± 12.86	30.09 ± 12.35	0.24

FSH – follicle-stimulating hormone; LH – luteinizing hormone; E_2 – estradiol

Table 2. shows the relationship between the mean values of sex hormones measured three times during hot flashes in women with hot flashes and mean values of sex hormones taken randomly three times during the day and night, in women without hot flashes. Women with hot flashes had significantly lower mean concentrations of FSH during the day, compared to controls (69.08 ± 28.84 IU/L vs. 107.18 ± 39.11 IU/L, $p < 0.01$) and during the night (60.72 ± 21.89 IU/L vs. 104.57 ± 38.06 IU/L, $p < 0.01$). Women with hot flashes had lower mean estradiol and LH levels during the day and night than women without hot flashes, but none of this differences were statistically significant.

DISCUSSION

Hot flashes occur as a result of changes in the concentrations of sex hormones that happen during menopause. Elevated concentrations of FSH and LH accelerate the depletion of number of follicles and reduce the synthesis of estrogen and inhibin, leading to vasomotor instability and emergence of hot flashes [7, 8, 9]. As estrogens are

essential for normal reproductive function, low concentrations of estrogen lead to a reduction in the number of ovulatory cycles and reduced fertility. In addition, low concentrations of estrogen and inhibin are not capable of overcoming the negative feedback of FSH and LH, leading to an even greater increase in the concentration of these hormones [10].

This study has shown that there is no difference in levels of FSH and LH in women with and without hot flashes. Dhanoya et al. [11] report that the higher FSH levels were significantly associated with the experience of hot flashes, and Mitchell and Woods [12] showed that hot flash severity was significantly associated with higher FSH and lower estrone levels. Meldrum et al. [9] indicated that LH levels increased significantly during hot flashes. Other studies have shown that there was no difference between the concentrations of FSH or LH in women with and without hot flashes, which was also obtained in the present study [13–17].

Despite these studies, FSH and LH are not thought to be the crucial etiological hormones involved in hot flashes. Many investigators hypothesize that changes in endogenous estrogen levels are the primary etiological factor for hot flashes [18, 19]. This hypothesis is supported indirectly by studies that show that estrogen replacement therapy reduces the number and intensity of hot flashes and directly by a few studies that show that women with hot flashes have lower estradiol levels than women without them, which was confirmed in this study, as well [8, 18–21]. Woods et al. [22] showed in their study that women with high severity hot flashes have lower levels of estrogen and higher levels of FSH. There are also studies that show no correlation between serum estradiol levels in women with hot flashes and women without them [13, 14, 16, 17, 23, 24].

After reviewing the literature, this is the first study measuring mean values of FSH, LH, and estradiol during the day and night episodes of hot flashes. In order to achieve more accurate level measuring, hormone values were measured three times during the day hot flash episodes and three times during the night hot flash episodes, and average value was then calculated. It was found that the mean daily and nocturnal value of FSH were lower in women with hot flashes, which can be explained by the fact that women without hot flashes were slightly younger than those without them. Women with hot flashes had lower mean estradiol and LH levels during the day and night than women without hot flashes, but none of these differences were statistically significant.

Whereas most studies have focused on the roles of FSH, LH, and estrogens in the etiology of hot flashes, a few studies suggest that other sex hormones may be involved. Gallicchio et al. [21] and Ratka et al. [25] found that progesterone levels were lower in the group of women with hot flashes than in women without them, which the present study did not confirm. As the levels of progesterone in both groups were anovulatory, this difference is not clinically relevant.

In this study, we obtained that women with hot flashes had higher prolactin levels than women without them, although the concentrations were in the normal value range. This could be explained by the fact that women who have hot flashes are more sensitive and vulnerable due to more activated sympathetic system. Similar results where shown in the study by Lambrinoudaki et al. [14].

Menopause is associated with a reduction in the overall synthesis of testosterone. Also, levels of androstenedione, DHEA, and its conjugate DHEA-S decline during menopause. This study has shown that the levels of DHEA-S were higher in women with hot flashes, while no difference in testosterone levels was found between these two groups. Øverlie et al. [8] showed in their study that women with hot flashes have higher levels of androstenedione, but there was no difference in testosterone and DHEA-S levels between women with and without hot flashes. Lambrinoudaki et al. [14] found no difference in testosterone and androstenedione levels between women with and without hot flashes; Kaya et al. [24] showed that there was no difference in testosterone and DHEA-S levels, and similar results were shown by Ratka et al. [25].

Low SHBG levels are correlated with increased risk of cardiovascular diseases [26]. Several studies found no differences in the SHBG levels between women with and without hot flashes, which was confirmed in this study [13, 14]. Randolph et al. [27] found that women with hot flashes have higher SHBG levels than women without hot flashes.

Although Øverlie et al. [8] showed that women with hot flashes have higher TSH levels, the mechanism that links the elevated TSH levels with the development of hot flashes is not yet known. Since TSH affects the metabolism of many hormones, including estradiol, we might assume that TSH increases metabolism of estradiol leading to hipoestrogenism. It is possible that TSH has a direct effect on the thermoregulatory center in the brain, thus enabling the emergence of hot flashes. Other studies found no difference in the concentration of TSH in women with hot flashes and in those without them, and the same result is demonstrated by our study [14, 17, 24].

CONCLUSION

To the best of our knowledge, this is the first study with hormone levels measured during hot flashes. We have found that women with hot flashes have significantly lower mean FSH levels during the day and night compared to the control group. They also had lower mean LH and estradiol during the day and night, although none of these differences were statistically significant. There was no statistically significant difference between basal levels of FSH, LH, and estradiol between these two groups of women.

Future studies should focus on dynamic assessment of hormone levels, meaning that they should be measured in shorter periods of time during the episodes of hot flashes in order to obtain more precise data.

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Вазомоторне вредности гонадотропина и естрадиола у менопаузи

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САЖЕТАК

Увод/Циљ Валунзи представљају један од првих клиничких симптома менопаузе. Механизам настанка валунга још увек није потпуно разјашњен. До терморегулаторне дисфункције доводе промене у концентрацијама циркулишућег фоликулостимулишућег хормона (ФСХ), лутеинизирајућег хормона (ЛХ), естрадиола и других хормона.

Циљ ове студије био је да испита повезаност динамске промене концентрације полних хормона и присуства вазомоторних симптома код жена у менопаузи.

Методе Испитивањем је обухваћено 36 жена подељених у две групе: у првој су биле 24 жене са валунзима, индекса телесне масе (ИТМ) 26,16 ± 3,42 *kg/m*^{2}, а у контролној групи 12 жена без валунга, ИТМ 26,82 ± 3,89 *kg/m*^{2}. Подаци о присуству валунга су добијени на основу анамнезних података. У крви су одређене базне вредности хормона: ФСХ, ЛХ, пролактина, естрадиола, прогестерона, тестостерона, глобулина који везује полне стероиде, дихидроепиандростерон-сулфата, тиреостимулишућег хормона и тироксина. Испитаницама са валунзима је узимана крв за одређивање вредности ФСХ, ЛХ и естрадиола током субјективног осећаја валунга у три узорка током дана и током ноћи.

Резултати Жене са валунзима су имале значајно више пролактин (389,58 ± 123,69 *mIU/L* према 258,19 ± 122 *mIU/L*; $p < 0,01$) и дихидроепиандростерон-сулфат (3,60 ± 2,49 *nmol /L* према 1,88 ± 1,27 *nmol /L*, $p < 0,05$) а ниже средње вредности ФСХ за време валунга током дана (69,08 ± 28,84 *IU/L* према 107,18 ± 39,11 *IU/L*; $p < 0,01$) и током ноћи (60,72 ± 21,89 *IU/L* према 104,57 ± 38,06 *IU/L*; $p < 0,01$).

Закључак Жене са валунзима су имале значајно ниже средње вредности ФСХ за време валунга током дана и током ноћи у односу на контролну групу.

Кључне речи: валунзи; менопауза; полни хормони