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Metabolic syndrome provides an insight into the possible physiologic mechanism(s) of climacteric hot flushes: A hypothesis of flush mechanism

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Climacteric is a more encompassing term that refers to the entire transition to the non-reproductive period of life. Hot flashes are one of the most common symptoms of climacteric and occur in the vast majority of postmenopausal women. Menopausal hot flashes manifest in form of peripheral vasodilatation and profuse perspiration. Although hot flashes clearly accompany estrogen withdrawal at menopause, the physiologic mechanisms for initiation of flushes and of transient physical changes during flush episodes remain elusive. Researchers targeted central-focus mechanisms in attempts to clarify the pathophysiology of hot flashes in postmenopausal women. In this article, we target a peripheral-focus mechanism. During data analysis of our unpublished work on "predictors and consequences of metabolic syndrome among postmenopausal Sudanese women", we observed that 75.8% of postmenopausal women with metabolic syndrome have hot flushes and sweating compared to 42.6% in postmenopausal women without metabolic syndrome. We thought that metabolic syndrome in postmenopausal women might give an insight to elucidate the pathophysiology of hot flashes, in general. We propose a hypothesis, during normal female reproductive period, a vasomotor tone on peripheral blood vessels is brought about by synergistic action of estrogen and catecholamines. This vasomotor tone is modulated by vasodilator effect of insulin. In postmenopausal women without metabolic syndrome, lack of estrogen results in peripheral vasodilatation. In postmenopausal women with metabolic syndrome, vasodilator substances released as a result of associated endothelial dysfunction override the insulin resistance effect on blood vessels. In postmenopausal women without metabolic syndrome the normally produced endothelial vasodilators potentiate the effect of insulin on blood vessels.

Keywords: Menopause, postmenopause, estrogen, catecholamines, insulin, vasodilatation

INTRODUCTION

Between the menarche and menopause, the female reproductive system undergoes cyclic changes called the menstrual cycle. The normal menstrual function results from complex interactions among the hypothalamus; which produces gonadotropin-releasing hormone (GnRH); the anterior pituitary gland which synthesizes and releases follicle stimulating hormone (FSH), lutenizing hormone (LH), and prolactin (PRL); the ovaries which synthesize and release estrogens, progesterone, and androgens; and associated target tissues such as the endometrium, cervix and the vaginal mucosa (1). Premenopause refers to the phase before menopause when the menstrual cycle is still regular after the age of 40, sometimes there is cessation of menstrual cycle (amenorrhoea) but not longer than three months. Perimenopause (the years immediately surrounding

menopause) precedes menopause by approximately four years and is characterized by menstrual irregularity, gradual increase in the number of anovulatory cycles, or amenorrhoea of at least three months but not longer than one year. A woman who has amenorrhoea for a full year or has a follicle stimulating hormone blood level is consistently elevated to 30 mIU/mL or higher is considered menopausal (2). Climacteric is a more encompassing term that refers to the entire transition to the non-reproductive period of life (1). Hot flashes are one of the most common symptoms of the climacteric and occur in the vast majority of postmenopausal women (3).The prevalence among naturally menopausal women has been reported to be 68% (4) to 82% (5) in the united states, 60% in Sweden (6), and 62% in Australia (7). The median age of onset is approximately 51 years (8). Among overectomized premenopausal women, the prevalence of hot flashes is approximately 90% (9). It was not until 1974 that a systematic investigation of the physiological nature of menopausal flushes was undertaken (10). Monlar carried out an elegant physiological study of hot flushes in a single subject and set the stage for a rapid growing field of neuroendocrine research. Hot flashes are characteristic of heat-dissipation response. They consist of sweating, peripheral vasodilatation, and sensation of heat centered on the face, then moving to the neck and chest, and finally becoming generalized (11). Although hot flashes clearly accompany estrogen withdrawal at menopause, estrogen alone is not responsible since levels do not differ between symptomatic and asymptomatic women (12). Menopausal flushes represent dysfunctional thermoregulation, initiated centrally in hypothalamic thermoregulatory nuclei. Peripheral vasodilatations with profuse perspiration are potent and characteristic components of heat loss mechanisms (13, 14). Pulsatile release of hypothalamic GnRH which initiates pituitary LH pulses, rather than LH itself, may be more directly associated with the dysfunction of thermoregulation during flushes. Taken together all the available evidence suggests that menopausal flushes have central origin involving neuroendocrine changes within the hypothalamus. The finding to date focus attention on the medial preoptic area, which is the major thermoregulatory nucleus in mammals (15), including man (16). This area also has high concentrations of estrogen progesterone receptors (17,18) suggesting that medial preoptic area neurons may be responsible to estrogen sensitization and withdrawal. The medial preoptic area is innervated by ascending noradrenergic neurons from the lateral tegmental noreponphrine system and locus coerulus in the brain stem (19). Thus a possible mediator of both GnRH and thermoregulatory changes during menopausal flushes is the catecholamine system, more specifically, the noradrenergic system. The observation that flashes occur after hypophysectomy suggests that the flashes are not due directly to LH release (20). In animals the hypothalamic GnRH has been found to fluctuate in hypophyseal portal vein blood (21).These fluctuations are thought to represent pulsatile secretion and are believed to be responsible in part for pulsatile LH release from the pituitary. It is possible that the GnRH or the hypothalamic factors responsible for its release may somehow alter the thermoregulatory centers of the hypothalamus resulting in initiation of hot flashes. The close proximity of some of GnRH neurons with thermoregulatory centers in the preoptic anterior hypothalamus is consistent with this concept (22). The observation that catecholamines play a role in central thermoregulatory function (23) and GnRH is also consistent with this hypothesis (24). There are few major risk factors for menopausal hot flashes. High body mass index is directly related to hot flash frequency (25) This may be caused by the effect of increased insulation from body fat, resulting in elevated core body temperature which triggers hot flashes (26). Cigarette smoking has also been found to increase the risk of hot flashes (27), possibly through the effect on estrogen metabolism or through thermogenic effect of nicotine (28). Although estrogen withdrawal unquestionably plays a major role in the development of menopausal flushes, the physiologic mechanisms for initiation of flushes and of transient physical changes during flush episodes remains elusive (29, 30).

MATERIAL AND METHODS

After permission and approval of the study from the relevant regional authorities, the aim of the study was explained to the participants. Written informed consent from participants was obtained.

Menopausal symptoms assessed in this study by using menopausal rating scale (MRS) questionnaire (31,32). The MRS developed by the Berlin center for epidemiology and health research in response to the lack of standardized scales to measure the severity of aging-symptoms and their impact on the health related quality of life. The MRS formally standardized according to psychometric rules. It consists of a list of 11 items assessing menopausal symptoms, divided into three subscales:

A. Somatic (hot flushes, heart discomfort, sleep problem, muscles and joint problems). B. Psycological (depression, irritability, anxiety, and physical and mental exhaustion. C. Urogenital (sexual problems, bladder problems, and dryness of vagina). The last two scales are beyond the scope of this work. Each item of these scales can be graded from 0-4, (0 = not present); (1= mild); (2 = moderate); (3 = severe); (4 = very severe). In order to facilitate analysis and interpretation of the result total scores in each area were 56, those who obtained scores less than 11 considered having no symptoms; 12-35 regarded as mild and moderate symptoms; and more than 35 considered to have sever and very severe symptoms (31, 32). A questionnaire was developed, pretested, validated and confidentiality was guaranteed.

Statistical analysis has been carried out using the software packages Microsoft Excel 2010, Epi Info 3.4.1 and SPSS for windows version 20 (SPSS Inc, Chicago IL).

Descriptive statistics carried out and the results reported as means ± standard deviations. Independent sample t-tests were conducted to assess the relationship between the metabolic syndrome and the studied variable (hot flushes). All statistical analyses were considered significant at a level of $P<0.05$.

RESULTS AND DISCUSSION

During data analysis of our unpublished work on "predictors and consequences of metabolic syndrome among postmenopausal Sudanese women", we observed that 113/149 (75.8%) postmenopausal women with metabolic syndrome have hot flushes and sweating compared to 60/141 (42.6%) (60) postmenopausal women without metabolic syndrome. Hot flushes are significantly higher in postmenopausal women with metabolic syndrome relative to those without the syndrome (Table 1).

Table 1: Hot flushes manifested among the postmenopausal women with and without metabolic syndrome.

Variables	Subjects with metabolic syndrome (n=149) Mean±SD	Subjects without metabolic syndrome (n=141) Mean±SD	P value
Hot flushes and sweating	3.01±.762	2.13±1.202	0.000

We thought that metabolic syndrome in postmenopausal women may help in understanding the pathophysiology of hot flashes, in general. Based on the modulatory effect of estrogen on adrenergic receptors in many tissues of the body (33), we propose a hypothesis: during normal female reproductive period, normal concentrations of estrogen elevate the resting membrane potential of smooth muscles of blood vessels of peripheral circulation. Resting membrane potential is the electrical potential which is equivalent to and opposing the chemical force of ions movement across cell membrane. It is primarily due to potassium efflux (34). The resting potential is brought closer to threshold potential. This priming depolarizing effect is a prerequisite for contraction of smooth muscles of blood vessels by catecholamines. Norepinephrine at basal level, interacts with alpha-1 receptors on surface of smooth muscles of blood vessels (35), is sufficient to promote the potential to threshold level with subsequent firing of action potential. This synergestic effect of estrogen and norepinephrine results in contraction of smooth muscles of blood vessels. This vasoconstrictor effect of norepinephrine is modulated by vasodilator effect induced by normal insulin concentration. Administration of insulin to obese, untreated, nondiabetic, hypertensive patients exerts a "small" blood pressure-lowering effect in these patients. These data strongly argue against the postulated pressor action of insulin in essential hypertension (36). Thus, the net result, of vasoconstriction induced by synergestic action of estrogen with norepinephrine and vasodilator effect induced by insulin, is slight contraction of smooth muscles of blood vessels which is responsible for normal diameter of blood vessels under resting condition. This tonic vasomotor tone is physiologically referred to as sympathetic tone (37). Thus our proposal claims that that sympathetic tone is not a responsibility of catecholamines only, it is a function of estrogen, catecholamines, and insulin. Since hot flashes accompany the decline of estrogens in the vast majority of naturally and surgically menopausal women, there is little doubt that they play a role in the genesis of hot flashes (38). However estrogens alone do not appear responsible for hot flashes since levels of estrogen in plasma (39), urine and vagina (40) do not correlate with the presence or absence of hot flashes. No difference in unconjugated plasma estrogen levels were found in symptomatic versus asymptomatic women (41). We propose, during climacteric, estrogen withdrawal will result into hyperpolarization of membrane potential of smooth muscles of blood vessels. That is to say the resting membrane potential is getting more negative. Catecholamines are no longer able to induce contraction of smooth muscles of blood vessels. In addition, insulin at normal concentration induces "unopposed" relaxation of smooth muscles of blood vessels. This results in cutaneous vasodilatation and hot flushes. Thus our proposal focuses on peripheral blood vessels. On their central- focus proposal, Robert and Freedman (42) proposed that hot flashes are triggered by core body temperature elevations acting within a greatly sympatheticaly reduced thermoneutral zone in symptomatic postmenopausal women. In homotherms, core body temperature is regulated between an upper threshold for sweating and a lower threshold for shivering. Between these thresholds is a neutral zone within which major thermoregulatory responses (sweating

and shivering) do not occur (43). Since estrogen modulates the adrenergic receptors in many tissues of the body including the brain (33), Freedman and Woodward (44) found that brain norepinephrine to be significantly higher in symptomatic than in asymptomatic postmenopausal women. In fact, brain norepinephrine increased significantly more during hot flashes (45). We suggest that both central and peripheral mechanisms work synergistically to induce hot flashes. This suggestion is supported by three important factors; first, the clinical studies which had shown that clonidine, an alpha-2 adrenergic agonist that reduces brain norepinephrine with consequent widening of thermoneutral zone, significantly reduced hot flash frequency (46, 47). Clonidine, in fact, did not completely abolish the flashes, probably, because it dealt only with the central mechanisms of flashes. Second, Freedman et al (48) showed that injection of yohimbine, an alpha-2 adrenergic antagonist that raises levels of brain noreinephrine, provoked hot flashes in symptomatic women and that injection of clonidine ameliorated them. Third, noradrenergic stimulation of medial preoptic area in monkeys (49) and baboons (50) by microionophoretic application of norepinephrine causes peripheral vasodilatation and heat loss and a drop in core body temperature similar to changes which occur in women during hot flushes. However, bradycardia and hypotension also occur in these animals indicating that adrenergic activation alone, at least in a single hypothalamic area does not produce a picture completely analogous to menopausal flushes (51). Since bradycardia and hypotension cannot be explained on basis of central alpha-2 adrenergic activity, a peripheral mechanism is likely to act directly on the heart and smooth muscles of blood vessels of peripheral circulation. In postmenopausal women with metabolic syndrome: lack of effect of estrogen on alpha-2 receptors results in release of more norepinephrine. However, the lack of sensitization of smooth muscles of blood vessels by estrogen will not allow vasoconstriction to occur. In case of postmenopausal women with metabolic syndrome, in addition to lack of estrogen, there is a linear association between the resistance to the effect of insulin on both glucose uptake and insulin induced vasodilatation in obese hypertensive patients (52). This insulin resistance will not allow vasodilator effect of insulin to be manifested. This could argue strongly against our proposal. However, the endothelial dysfunction in patients with metabolic syndrome is associated with production of vasodilator substances (53) that lead to hot flushes. It seems that in postmenopausal women without metabolic syndrome the normally produced endothelial vasodilators act synergistically with insulin to promote vasodilatation. While in postmenopausal patients with metabolic syndrome the pathological endothelial vasodilators overreide the insulin resistance effect on blood vessels. This results into hot flushes.

In conclusion, we target a peripheral-focus mechanism in an attempt to understand the pathophysiology of hot flushes mechanism in postmenopausal women. In postmenopausal women without metabolic syndrome, lack of estrogen results in peripheral vasodilatation. In postmenopausal women with metabolic syndrome, vasodilator substances released as a result of associated endothelial dysfunction override the insulin resistance effect on blood vessels. In postmenopausal women without metabolic syndrome the normally produced endothelial vasodilators potentiate the effect of insulin on blood vessels. Research is warranted to explore the differential action of endothelial vasodilators, both under normal and pathologic conditions, on smooth muscles of peripheral blood vessels.

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