Clinical Symptoms and Quality of Life: Hot Flashes and Mood

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Plácido Llaneza

4.1 Introduction

Health-related quality of life (HRQoL) is a subjective parameter which refers to the effects of an individual's physical state on all aspects of psychosocial functioning. It is defined as the value assigned to duration of life as modified by impairments, functional states, perceptions, and social opportunities that are influenced by disease, injury, treatment, or policy [1]. The specific domains of HRQoL include resilience or the capacity to respond to stress, health perceptions, physical functioning, and symptoms. Menopausal changes could affect HRQoL. Some domains of HRQoL may improve after menopause, but several transversal and longitudinal studies have reported negative effects of menopausal symptoms in HRQoL and the severity of menopausal symptoms is what reflects best the profile of quality-of-life dimensions [2–4].

Hot flushes (HF) and night sweats (NS) are the predominant symptoms of menopause and they are usually referred as vasomotor symptoms (VMS) because of the vascular reactivity with initial prominent vasodilatation and subsequent vasoconstriction associated to estrogen withdrawal [5]. Although women describe episodes similar to menopausal VMS at various stages of their reproductive life cycle, it is estimated that at some point during the menopausal transition, up to 80% of women will experience HF [6].

The prevalence of VMS varies widely and may be influenced by a range of factors, including climate, diet, lifestyle, women's roles, and attitudes regarding the end of reproductive life and aging [7–9]. A lower prevalence in Japanese and South-East Asian women was found, being reported only by 5–18% of postmenopausal

P. Llaneza
Department of Obstetrics and Gynecology, Asturias Central University Hospital, University of Oviedo, Asturias, Spain
e-mail: llaneza@uniovi.es

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women [10]. However, enormous differences in the experience of VMS have also been identified among women within the same culture [11].

HF may occur at any time of day or night and be spontaneous or triggered by a variety of common situations such as embarrassment, sudden ambient temperature change, stress, alcohol, caffeine, or any warm drink. The subjective features are individual and variable, but usually start with a sudden sensation of heat or warmth, often accompanied by sweating, some reddening of the skin, and sometimes palpitations. Most often this will start in the upper body and spread upwards or downwards, and infrequently all over the body. The perceived duration of HF ranges from 30 s to 60 min, with a mean between 3 and 4 min [12].

4.2 Pathogenesis

Pathogenesis of VMS still remains unknown. The mechanisms of increases in skin blood flow during HF may include the withdrawal of sympathetic vasoconstrictor activity, increases in sympathetic cholinergic vasodilator activity, or a combination of both neural mechanisms and nonneural factors [13, 14]. Peripheral estrogen levels do not differ between symptomatic and asymptomatic women, but symptomatic women have higher levels of central noradrenergic activation than asymptomatic women and elevated central noradrenergic activation narrows the thermoneutral zone [15], so the heat dissipation responses are triggered if the core body temperature crosses the upper threshold of the thermoneutral zone [5, 16] (Fig. 4.1).

There is evidence concerning the implication of central neuropeptides. In the hypothalamus of postmenopausal women, there are dramatic changes in morphology and neuropeptide gene expression in the infundibular (arcuate) nucleus. Autopsy

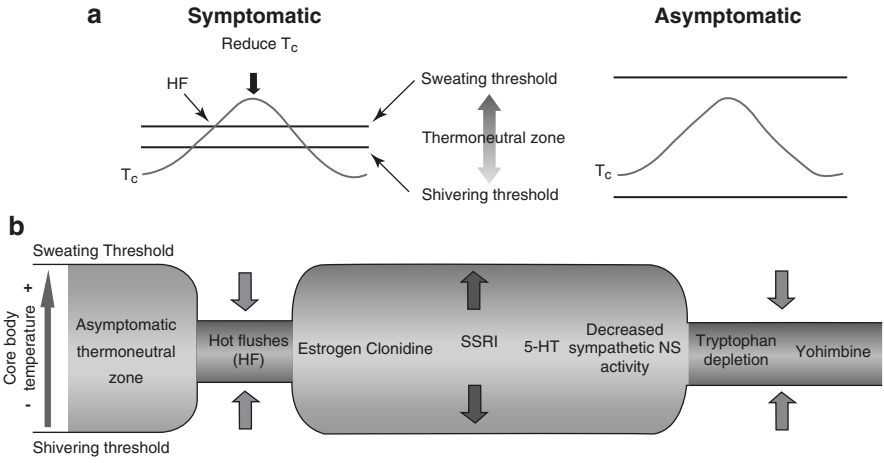

Fig. 4.1 Mechanism of HF production, according to Freedman et al. [70] and Archer et al. [5]. (**a**) Small core body temperature (T_c) elevations acting within a reduced thermoneutral zone trigger hot flushes (HF) in symptomatic postmenopausal women; (**b**) the factors that influence the thermoneutral zone. *SSRI* selective serotonin reuptake inhibitor, *5-HT* serotonin, *NS* night sweat

studies showed that these neurons increase in size (hypertrophy) accompanied by increased neurokinin B (NKB) and kisspeptin gene expression [17]. The hypertrophied neurons express estrogen receptor alpha [18], and are called KNDy neurons based on the coexpression of kisspeptin, NKB, and dynorphin [19–21]. Nearly identical changes occur in young monkeys in response to ovariectomy and the changes are reversed by estrogen replacement [20, 22]. These data provide compelling evidence that hypertrophy and increased NKB and kisspeptin gene expression in postmenopausal women are due to estrogen withdrawal.

Men and women with mutations in kisspeptin, NKB, or their receptors exhibit hypogonadotropic hypogonadism [23–25]. They do not go through puberty, are infertile, and secrete insufficient LH resulting low levels of sex steroids. Thus, KNDy neurons express two peptides that are essential for human reproduction. Basic research in multiple species (including human) has established a role for KNDy neurons in regulating pulses of GnRH into the portal capillary system [26–29]. The close timing of LH pulses with hot flushes provides a clue that estrogen-responsive KNDy neurons could play a role in the generation of flushes [30].

To determine if KNDy neurons could play a role in thermoregulation, a series of studies were performed using a rat model (for a review, see [31]). Anatomical studies showed projections of KNDy neurons to the median preoptic nucleus (MnPO), an important component of the CNS pathway that regulates heat dissipation effectors [32, 33]. Moreover, MnPO neurons express the neurokinin 3 receptor (NK_3R), the primary receptor for NKB [34]. These data provide an anatomic framework to understand how estrogen-responsive KNDy neurons could specifically interface with hypothalamic brain areas that regulate heat dissipation effectors. Further studies using a rat model showed that KNDy neurons influence cutaneous vasodilation (flushing) via projections to NK_3R-expressing neurons in the MnPO [34–36].

Clinical studies have provided strong support for the hypothesis that KNDy neurons participate in the generation of hot flushes via NK_3R signaling. For example, infusion of NKB into the peripheral circulation induces hot flushes in women [37]. Moreover, genetic variation in the gene encoding the NK_3R receptor is associated with hot flushes in women [38]. More recently, two clinical trials have shown that treatment with an NK_3R antagonist successfully reduces the number and severity of hot flushes [39, 40]. These studies open up a new avenue for treatment of hot flushes with targeted therapies that do not require estrogen replacement.

4.3 Duration of HF

It is accepted that HF persisted for about 6 months to 2 years for most women, but recent studies of the duration of HF indicate that women can expect HF to continue, on average, for nearly 5 years after the final menstrual period, while more than one-third of women who experience moderate/severe hot flushes will continue to have them for more than 10 years after the menopause [41]. The expected duration of menopausal VMS is important to women making decisions about possible treatments. In the Study of Women's Health Across the Nation (SWAN) carried out in a sample of 3302 US women enrolled during menopausal transition, the median total VMS

duration was 7.4 years with some factors related to longer duration as race/ethnicity, younger age, lower educational level, greater perceived stress and symptom sensitivity, and higher depressive symptoms and anxiety at first report of VMS [6]. Duffy et al. reported that women resilient to HF were those who had previously not been bothered by their menstrual periods; were not experiencing somatic symptoms or night sweats; and perceived their symptoms as having low consequences on their lives and women resilient to NS were nonsmokers, were not experiencing sleep difficulties, were not using psychological symptom management strategies, and perceived their menopausal symptoms as having low life consequences [42]. Moreover, Perez-Lopez et al. [43] in other study aimed to assess resilience, depressed mood, and menopausal symptoms in a sample of Spanish postmenopausal women have also reported that depressed mood and participation in regular exercise correlate with lower and higher resilience to menopausal symptoms, and depressed mood was associated with the severity of menopausal symptoms (somatic and psychological).

4.4 Hot Flushes, Depressed Mood, and Quality of Life

The impact of VMS on quality of life may be considerable and is often underestimated. VMS may interfere with work and daily activities as well as with sleep, causing subsequent fatigue, loss of concentration, and mood changes, all of which can interfere with family life, sexual function, and partner relationships affecting HRQoL [5, 44]. The impact of untreated HF on quality of life was studied in a sample of 252,000 working women with untreated HF compared to asymptomatic age-matched women. During a 12-month period, the women with hot flashes showed increased work loss, 1.1 million extra medical visits, and a health insurance bill almost $400,000,000 more compared to the asymptomatic women [45].

HF are linked to vascular changes, cardiovascular risk, and changes in the brain, with increased white matter hyperintensities suggesting that the relationship between hot flashes and cardiovascular risk observed in the periphery may extend to the brain [46, 47]. In this sense, episodes of HF are often accompanied by a feeling of irritation, anxiety, or panic that may significantly compromise overall health and decrease cognitive function [3, 48]. In a systematic review of the literature a bidirectional association between VMS and depressive symptoms has been reported in women presenting to menopause clinics [49]. Moreover, according to a recent meta-analysis, perimenopause is a phase particularly vulnerable for developing depressive symptoms and there are indications that VMS are positively related to depressive symptoms during menopausal transition [50].

Burleson et al. [51] in a study using multilevel structural equation modeling for testing whether changes in daily VMS occurrence predicted changes in occurrence of same-day sleep problems and changes in next-day positive and negative mood ratings and whether sleep problems mediated any predictive effect of symptoms on next-day mood found, after controlling for initial depression, that daily VMS predicted same same-day sleep problems and next-day positive mood, although significant direct relationships between VMS and mood were found primarily only in women with initial depression scores in the low to moderate range. The authors

suggested that any effect of VMS on mood may occur largely through a mechanism other than sleep disruption. However, Pinkerton et al. [52] in another placebo-controlled phase 3 trial using the Menopause-Specific Quality of Life (MSQoL) questionnaire found that frequency and severity of HF showed approximately linear relationships with MSQOL and sleep parameters. Lastly, Katon et al. [4] in a large sample of veteran and non-veteran US postmenopausal women found that any VMS was associated with decreased HRQoL and baseline depression and obesity amplified the negative association between VMS and HRQoL (Fig. 4.2).

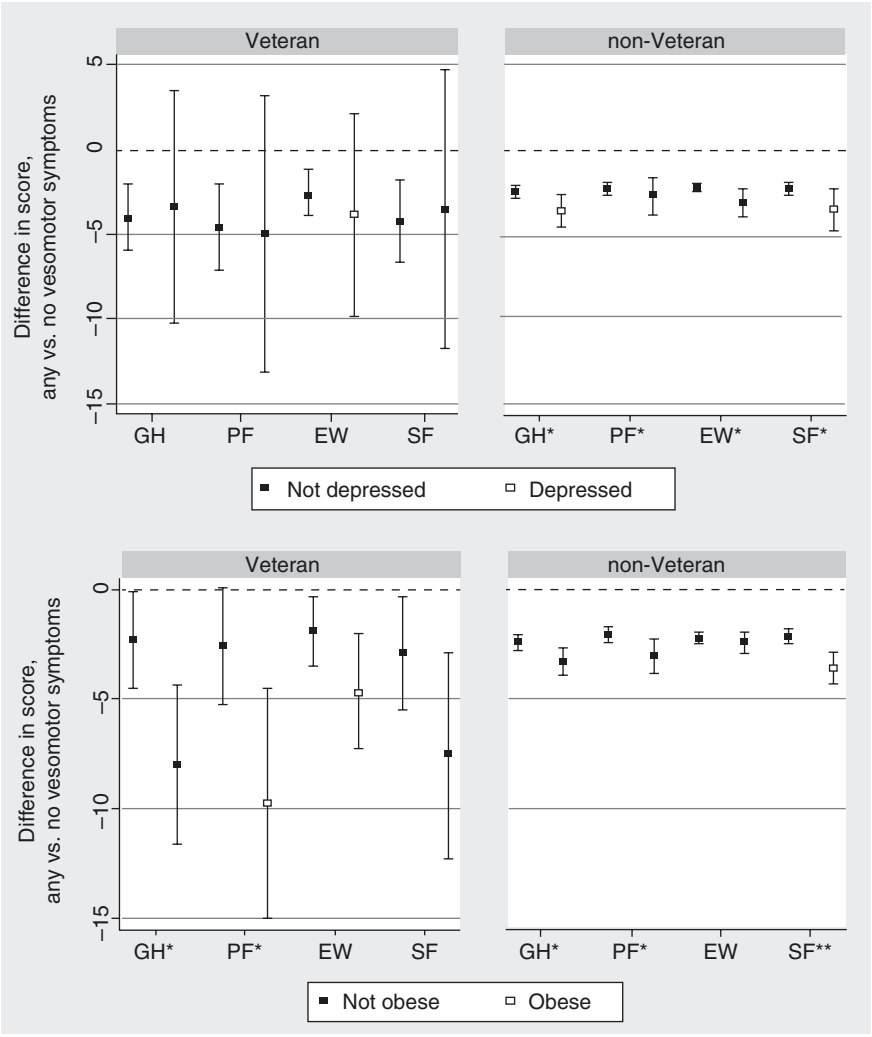

Fig. 4.2 Mean differences in health-related quality of life (HRQoL) subscales at year three follow-up associated with any vasomotor symptoms (VMS) at baseline among veteran and non-veteran women, by depression status and obesity. *GH* general health, *PF* physical health, *EW* emotional well-being, *SF* social functioning [4]

Depressed mood symptoms and other depressive disorders are common among middle-aged women. Women are more vulnerable than men to depressive disorders [53] and endocrine influences have been postulated [54–56] but the effect of hormonal changes on depression and depressed mood remains unclear due to differences in coping style and response to stress or gender differences in socialization may also lead to higher rates of depression in women [55, 57]. Risk factors for the development of depressive symptoms and depression in the menopausal transition include the presence of VMS, as well as a personal history of depression (particularly depression that is related to pregnancy or hormonal changes through the menstrual cycle), surgical menopause, adverse life events, and negative attitudes to menopause and ageing [58]. Some studies have found that women with climacteric symptoms (VMS, vaginal dryness, and dyspareunia) are more likely to report negative affect, anxiety, and/or depressive symptoms [59, 60] and the risk for new-onset depression is heightened by more severe VMS [61]. In a small Swedish study anxiety and depression were significantly greater in women with surgical premature ovarian insufficiency [62] and Kronenberg et al. [63] reported that depressed feelings during HF were more common in women after surgical menopause than with natural menopause and that suicidal thoughts during HF occurred almost twice as often (10%) in these women. However, not all studies report psychological disorders related to menopause [64] and other factors as biopsychosocial and partner factors could also have a significant influence on middle-aged women's sexuality and depressive disorders. Stress, educational level, ethnicity, socioeconomic factors, and partner status may also influence the prevalence and clinical course of both menopause symptoms and depressive disorders [55].

4.5 Hot Flushes Management with Antidepressant Drugs

Hormonal therapy (HT) reduces the frequency and severity of HF, with health benefits when started near menopause, particularly for women with early menopause. It carries small absolute risks, and has potential health benefits on reduction of heart disease and all-cause mortality for women younger than 60 years and within 10 years of menopause [65]. However, long-term health risks in some women receiving hormone therapy for VMS were reported by the Women's Health Initiative and Million Women Study [66, 67]. Although data strongly support using HT in symptomatic women started near menopause, societal factors overwhelm the findings and the use of HT has declined in a sustained fashion and some menopausal symptomatic women are treated with nonhormonal therapy.

Several nonhormonal therapies were found effective for HF over placebo include some antidepressant drugs as serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SSNIs), and gabapentin. Fluoxetine, paroxetine, citalopram, escitalopram, venlafaxine, desvenlafaxine, gabapentin, and pregabalin, as well as low-dose paroxetine salt, have shown significant reductions in HFs over placebo [68, 69]. However, doses and the incidence of side effect as nauseas,

dizziness, or even suicidal ideation when are used in higher doses as an antidepressant must be considered.

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