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Vasomotor symptoms and metabolic syndrome

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ABSTRACT

A vast majority of menopausal women suffer from vasomotor symptoms, such as hot flushes and night sweats, the mean duration of which may be up to 7–10 years. In addition to a decreased quality of life, vasomotor symptoms may have an impact on overall health. Vasomotor symptoms are associated with overactivity of the sympathetic nervous system, and sympathetic overdrive in turn is associated with metabolic syndrome, which is a known risk factor for cardiovascular disease. Menopausal hot flushes have a complex relationship to different features of the metabolic syndrome and not all data point towards an association between vasomotor symptoms and metabolic syndrome. Thus, it is still unclear whether vasomotor symptoms are an independent risk factor for metabolic syndrome. Research in this area is constantly evolving and we present here the most recent data on the possible association between menopausal vasomotor symptoms and the metabolic syndrome.

Contents

1. Introduction

Up to 80% of menopausal women suffer from vasomotor symptoms. Follow-up studies [1–3] have shown that the mean duration of vasomotor symptoms is longer than previously thought, up to 7–10 years. Despite the fact that vasomotor symptoms are very common, the precise etiopathology behind them is still unclear. Vasomotor symptoms are a profound physiological reaction to hypoestrogenism due to the decline in ovarian function and they are also associated with an overactivity of the sympathetic nervous system [4]. The decrease in endogenous estradiol, either through surgical or natural menopause, and an elevated central sympathetic tone, mediated through alpha-2 adrenergic receptors, are associated with a narrowed thermoneutral zone in the thermoregulatory center in the brain. These changes in temperature regulation in symptomatic women cause small increases in core body temperature to trigger vasomotor symptoms, such as hot flushes and night sweats [4].

An abundance of evidence link chronic activation of the sympathetic nervous system and metabolic disturbances [5]. Elevated

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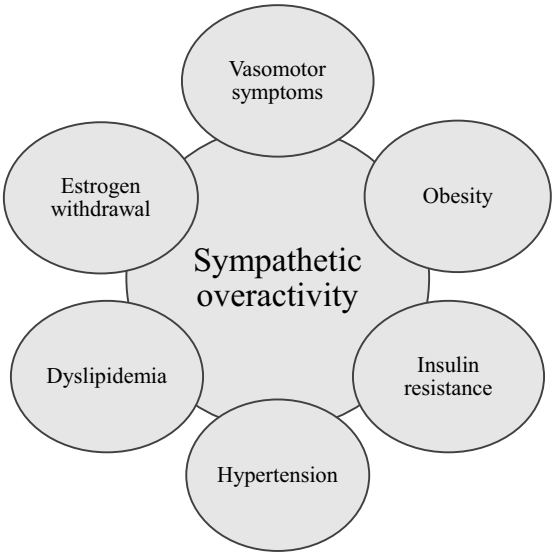

Complex interplay between vasomotor symptoms, estrogen withdrawal and different features of the metabolic

Fig. 1. Complex interplay between vasomotor symptoms, estrogen withdrawal and different features of the metabolic syndrome. Based on [4,5,8].

sympathetic tone may result in altered vascular function [6], changes in blood pressure [7] and lipids [8], and development of insulin resistance [5]. The metabolic syndrome (MetS) is a cluster of closely related risk factors for cardiovascular disease and type 2 diabetes. These include increased blood pressure, dyslipidemia (raised triglycerides and lowered high-density lipoprotein cholesterol), hyperglycemia and central obesity [9]. Prothrombotic and proinflammatory states and insulin resistance are also related to MetS. The prevalence of MetS is increasing rapidly in line with the growing obesity epidemic [10]. Although weight gain at midlife is not primarily influenced by menopause [11], the hormonal changes are associated with increased total and abdominal fat [12–14]. These changes in the body composition are a risk factor for insulin resistance and the progression of type 2 diabetes. Furthermore, abdominal obesity may be related to an adverse lipid profile.

Vasomotor symptoms and MetS share a common nominator, sympathetic overactivity (Fig. 1). Thus, menopausal women with vasomotor symptoms could well be at risk for MetS. On the other hand, MetS may also exacerbate sympathetic overdrive [15] and perhaps worsen vasomotor symptoms. Obesity is a mediator both in vasomotor symptoms and MetS and its' interactions and the endocrine functions of the adipose tissue are targets for an abundance of research. In this review we present the most recent findings on vasomotor symptoms and the MetS, especially with regard to the persistence or severity of hot flushes and the role of the adipose tissue.

2. Vasomotor symptoms and blood pressure

Menopause-associated alterations in the function of the autonomic nervous system may contribute to the increase in blood pressure [7]. According to a recent systematic review with pooled analysis (12 studies, 19 667 women) published in this Journal [16] in 2015, systolic blood pressure tended to be higher in women with hot flushes (mean difference 1.95 mmHg, 95% CI 0.27-3.63) or night sweats (mean difference 1.33 mmHg, 95% CI, 0.63-2.03). For diastolic blood pressure, only night sweats were associated with a higher mean (mean difference 0.55 mmHg (95% CI, 0.19–0.91), when compared with women with no symptoms. Hot flushes *per se* did not confer an increased odds for hypertension, but night sweats were associated with a higher odds of hypertension compared to those without (OR 1.17, 95% CI: 1.04–1.31, one study) [16].

Not all cross-sectional data are uniform on the detrimental effects of vasomotor symptoms and blood pressure. One study actually found that women with most frequent vasomotor symptoms during 24 h had lower systolic blood pressure [17]. Also data on no association between vasomotor symptoms and blood pressure exist e.g. [18]. Looking at different menopausal stages, the effect of vasomotor symptoms on blood pressure seems mixed. In a cross-sectional study on 590 perimenopausal women there was no association between vasomotor symptoms and blood pressure [19]. In another study both systolic and diastolic blood pressures were significantly higher in women with vasomotor symptoms either <10 years or ≥10 years postmenopausal, when compared with women without symptoms [20]. Of note, women in both studies [19,20] showing increased blood pressure with vasomotor symptoms were overweight with a mean BMI between 26 and 29 kg/m^2. On the contrary, women in studies [17,18] showing lack of association were lean with a mean BMI ≤25 kg/m^2.

As vasomotor symptoms tend to last for several years, the possible impact on different markers for cardiovascular disease may be best studied in a longitudinal setting. One of the recent reports from the SWAN study elaborate on the association between vasomotor symptoms and blood pressure [21]. In this study data on vasomotor symptoms and blood pressure was collected at each annual study visit. The study included 2839 women and mean follow-up was 8.2 years. Women with ≥6 days with vasomotor symptoms during the preceding two weeks had greater increases in diastolic blood pressure over time than did asymptomatic women, or those with less symptoms. Also the risk of developing pre-hypertension or hypertension during follow-up was increased among these women (hazard ratio of 1.39, 95% CI; 1.09–1.79) even after adjustment for multiple covariates [21].

It seems that vasomotor symptoms may be associated with increased blood pressure. However, obesity may be a factor that modulates this effect. More data are also needed regarding the impact of the severity of vasomotor symptoms on blood pressure.

3. Vasomotor symptoms and lipids

In accordance with blood pressure, vasomotor symptoms starting already in premenopause may not associate with lipids, glucose levels or insulin sensitivity [22]. This was detected in a Canadian 4-year follow-up study (n = 80) where vasomotor symptoms were