

Vasomotor Symptoms: More Than Temporary Menopausal Symptoms

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Vasomotor symptoms (VMS), such as hot flashes and night sweating, are classic menopausal symptoms experienced by a majority of perimenopausal and postmenopausal women. VMS have received a great deal of attention due to their relationship with cardiometabolic risk. Further, accumulating evidence indicates that VMS are associated with an increased risk of several chronic diseases, including metabolic syndrome, type 2 diabetes mellitus, nonalcoholic fatty liver diseases, and osteoporosis in perimenopausal and postmenopausal women. These findings suggest VMS as biomarkers of impaired cardiometabolic conditions rather than just temporary symptoms in menopausal women, warranting further studies to confirm the casual relationship of VMS with these diseases and the exact underlying mechanism in this context.

Key Words: Cardiovascular diseases, Hot flashes, Menopause, Metabolic syndrome, Vasomotor symptoms

INTRODUCTION

Due to the increase in average life expectancy, mainly in developed countries, most women spend more than one-third of their lifetime in a postmenopausal state. The mean life expectancy at birth of Korean women was 85.7 years in 2018, 2.4 years longer than that in Organisation for Economic Co-operation and Development countries [1]. Health management and quality of life during the postmenopausal period have received more attention in recent years. Vasomotor symptoms (VMS) in particular, such as hot flashes and night sweating, are major issues experienced by menopausal women (Fig. 1); in fact, 50% to 75% of perimenopausal and postmenopausal women experience some degree of VMS during their lifetime [2]. Unlike traditionally, where VMS were regarded as transient symptoms of perimenopause, recent studies have suggested that VMS can persist for more than seven years after onset



Fig. 1. Vasomotor symptoms in menopausal women.

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of menopause [3]. International guidelines recommend hormone replacement therapy (HRT) for management of VMS in selected cases [4,5]. Based on recent findings on the role of kisspeptin/neurokinin B/dynorphin neuron, a modulator of gonadotropin-releasing hormone secretion, in the physiology of VMS, neurokinin 3 receptor antagonists stand out as a novel treatment option for VMS, and ongoing clinical trials are aiming to confirm their efficacy [6].

Postmenopausal women are at a higher risk of developing several chronic diseases, including obesity, metabolic syndrome, cardiovascular diseases (CVDs), and osteoporosis, than premenopausal women independent of age [7]. Decreasing sex hormone levels during menopause have been collectively considered a key factor in the association between these chronic diseases and menopause; however, the exact mechanisms underlying these associations remain unclear. Recent accumulating evidence indicates that VMS are not only bothersome symptoms of menopausal transition, but also indicators of risk of the aforementioned chronic diseases and related conditions. Epidemiologic studies conducted by our study group have shown that presence or severity of VMS is associated with increased risk of metabolic syndrome, insulin resistance, nonalcoholic fatty liver disease (NAFLD), and osteoporosis [8-10]. However, the exact underlying mechanisms of those associations are unclear, and many confounding factors require consideration, such as age, obesity, and lifestyle choices [11].

This study aimed to review previous investigations of the associations between VMS and chronic diseases among perimenopausal and postmenopausal women and to identify whether VMS collectively are an independent risk factor for those diseases. Further, our review aimed to examine whether VMS collectively could be an indicator of those diseases and be addressed to prevent and reduce patient risk.

VMS AND OBESITY

Previous studies have suggested that obesity might have a protective effect against VMS because androgens are aromatized into estrogens by aromatase cytochrome P450 in adipose tissue [12]. However, recent accumulated evidence showed that women with obesity are more likely to report VMS than lean women [13,14]. A subcohort of a large-sized, longitudinal cohort study suggested that the association between VMS and obe-

sity may change with menopausal stage (e.g., positive association at early menopausal transition, inverse association at late menopausal transition) [15]; however, these findings need to be confirmed by further epidemiologic studies.

One of the generally accepted hypotheses for these associations is that the insulating effect of increased body fat in women with obesity can raise the core body temperature and may facilitate the association between obesity and VMS [16]. Another suggested hypothesis is that chronic inflammation in adipose tissue triggered by obesity may negatively affect ovarian function and induce VMS in the menopausal transition [17]. Supporting this hypothesis, it was shown that leptin, a proinflammatory adiponectin, is associated with VMS, whereas anti-inflammatory adiponectin was not [18]. Further, abundant body fat may influence the central nervous system and increase sympathetic tone, i.e., the thermoregulatory variable contributes to an increase in hot flashes [19]. However, these explanations have not yet been verified, and the exact underlying mechanism of the association between obesity and VMS should be revealed by further investigations.

VMS AND METABOLIC SYNDROME

Metabolic syndrome constitutes a group of metabolic abnormalities including increased blood pressure, increased triglyceride level, decreased high-density lipoprotein (HDL) cholesterol level, hyperglycemia, and central obesity that increase an individual's risk of CVDs and diabetes mellitus (DM) [20]. The prevalence of metabolic syndrome is increasing both worldwide and in Korea due to changing lifestyle [21]. Menopause is a well-known risk factor of an increased prevalence of metabolic syndrome independent of age [22]. Further, several epidemiologic studies have reported that postmenopausal status is associated with increased risk of metabolic syndrome as well as VMS in menopausal women [7,11,14]. However, most existing studies on these relationships are limited by small population size or cross-sectional study design. Thus, the causal relationship and underlying mechanism should be elucidated in further studies.

According to the accumulated evidence, menopausal VMS are diversely associated with each component of metabolic syndrome. Our study group reported the results of a cross-sectional study of 1,906 Korean postmenopausal women suggesting that the presence

of VMS is associated with increased risk of metabolic syndrome after adjustment for confounding factors [14]. Further, lipid abnormalities and central obesity are important metabolic components associated with these symptoms [14]. In a previous study involving data from the Korean National Health and Nutrition Examination Survey, both lipid abnormalities and central obesity were major factors related to increased prevalence of metabolic syndrome in the Korean population over the past 10 years [21]. Further studies on the association between VMS and metabolic syndrome in Korean women may require an emphasis on these two metabolic components. In the Study of Women's Health Across the Nation (SWAN), the presence and frequency of VMS were associated with higher triglyceride, low-density lipoprotein cholesterol, and HDL cholesterol levels [23]. Of note, night sweats were associated with abnormal lipid profiles in menopausal women in a previous epidemiological study [24]. Although the correlation between VMS and obesity has been repeatedly reported, it should be further studied in relation to central obesity, body mass index (BMI)-defined obesity, and visceral obesity, which may be diversely related to metabolic diseases [25]. There is evidence of association between VMS and high blood pressure [26] and insulin resistance [10]; however, these findings should be confirmed with large studies.

Several mechanisms linking VMS and metabolic syndrome have been suggested. A decreased endogenous serum estrogen level in the menopausal period seems to be linked with several metabolic impairment profiles; however, it cannot explain the pathophysiology of VMS [27]. Separately, chronic sympathetic nervous system activation is associated with a narrowed thermoneutral zone in the brain that may cause VMS and result in metabolic disturbances including altered vascular function, changes in blood pressure and lipid level, and insulin resistance [11]. Obesity is a representative shared determinant factor of VMS and metabolic syndrome, although the association between them remained after adjustment for obesity or BMI [14]. However, evidence supporting these hypotheses is insufficient, and further investigations are warranted.

VMS AND DM

According to a previous study that prospectively examined the association between VMS and incident diabetes among 150,007 postmenopausal Women's Health

Initiative participants from 1993 to 2014, VMS was associated with an 18% increase in diabetes risk (95% confidence interval, 1.14–1.22), while VMS severity was similarly associated with the risk of diabetes [28]. Of note, these associations remained following adjustment for obesity and were more pronounced in women reporting night sweats together with hot flashes than for those reporting hot flashes only [28]. An association between VMS and insulin resistance, a precursor of diabetes, was also reported by several epidemiologic studies [10,29]. In the SWAN study cohort of 3,075 women with eight years of follow-up, hot flashes were correlated with a higher homeostatic model assessment of insulin resistance score, a measure of insulin resistance, independent of estradiol level [29]. Obesity, sleep disturbance, and sex hormone level changes were suggested as linking factors, but the supporting evidence available to date is not sufficient. Mainly due to the small number of previous studies on the association of VMS with DM or insulin resistance, this issue requires elucidation in further large-scale studies.

VMS AND CARDIOVASCULAR RISKS

Nearly half of all deaths in women over 50 years of age are associated with CVDs [30]. Screening of high-risk populations and implementation of effective primary prevention measures are the most important health-care priorities. The association between menopause and increased risk of CVDs in women has been well-described [31], and that between menopausal VMS and CVDs has also been repeatedly reported in more recent studies, although there is no casual evidence. A prospective cohort study of 11,725 women aged 45 to 50 years demonstrated that women with frequent VMS were at increased risk of developing coronary heart disease over 14 years after adjustment for age, menopause status, lifestyle, and other chronic diseases [32]. The SWAN study, one of the largest health studies among menopausal women, showed that women with VMS had indices of greater subclinical CVDs, including poorer endothelial function and poorer flow-mediated dilation, as well as greater aortic calcification and carotid artery intima media thickness (IMT) relative to women without VMS [33]. A recent large-scale meta-analysis assessing association between VMS and various cardiovascular risk markers also showed that VMS are associated with increased risk of CVDs, although this correlation was attenuated after adjustment for car-

diovascular risk factors [34]. Sympathetic activation is the most frequently suggested mechanism linking VMS with CVDs. Chronic activation of the sympathetic nervous system seems to be associated with altered vascular function, changes in blood pressure and lipids, and development of insulin resistance [11].

Recent research, on the other hand, suggests that, apart from traditional CVD risk factors, relations between VMS and CVD risk are sensitive to timing and duration of VMS. In one study, the early-onset VMS group showed greater IMT results, which is a measure of subclinical CVDs [35]. In addition, women with a longer duration of VMS also experience more severe aortic calcification later in life [36]. The findings linking VMS and subclinical CVDs indicate that VMS occurring in early menopausal years and having a longer duration are associated with higher CVDs risk. Still, critical questions like the association of the mechanism of VMS as a marker of CVDs risk remain. Furthermore, relations between VMS and CVDs risk are not yet clear, so whether VMS are markers, cofactors, or part of a causal pathway of CVDs should be clarified. Future studies are warranted to reveal the exact mechanism of this correlation. For treating VMS, hormone therapy, e.g., supplementing estrogen, is considered the most effective method, but patients in this context could develop CVDs adversely, so the VMS and CVDs risk correlation should be judged carefully [37].

VMS AND NAFLD

NAFLD is a spectrum of liver disorders defined by the presence of excessive lipid accumulation, referred to as steatosis, in more than 5% of hepatocytes, with little or no alcohol consumption [38]. Menopause and low estrogen level have been reported to be risk factors of NAFLD [39]. Considering that NAFLD is a hepatic manifestation of metabolic syndrome and insulin resistance [40], and that VMS are correlated with those diseases, an association between VMS and NAFLD can be expected. However, few studies have examined the association between VMS and NAFLD. In a cross-sectional study of 1,793 menopausal Korean women, moderate to severe VMS was significantly associated with risk of NAFLD (odds ratio, 1.50; 95% confidence interval, 1.10–2.03) following adjustment for confounding factors including central obesity and insulin resistance [9]. Regarding the association between VMS and metabolic syndrome, obesity, sympathetic overactivity,

and hypoestrogenism have been suggested as potential underlying mechanisms linking NAFLD and VMS [41]; however, evidence in this regard is lacking. Further longitudinal studies are warranted to confirm the association between VMS and NAFLD among menopausal women.

VMS AND OSTEOPOROSIS

Osteoporosis is a well-known chronic disease that is aggravated in menopausal women due to decreased serum estrogen level [42]. Previous large epidemiologic studies have consistently reported that middle-aged women with VMS had lower bone mineral density at the lumbar spine and/or femoral neck bone than did women without VMS [8,43-45]. However, other studies have presented conflicting results regarding this association [46]. Nevertheless, it is noteworthy that estrogen-based HRT for menopausal women with VMS can improve bone density or fracture risk [47]. Further clinical studies are needed to demonstrate that HRT may be a first-line therapy for prevention and/or treatment of osteoporosis in certain menopausal women with VMS.

CONCLUSION

Several previous studies have indicated that menopausal VMS are associated with increased risk of chronic diseases such as metabolic syndrome, type 2 DM, CVDs, NAFLD, and osteoporosis in perimenopausal and postmenopausal women (Fig. 2). Menopausal VMS are expected to be useful biomarkers or predictors of cardiovascular risk and these chronic diseases rather than just temporary symptoms in menopausal women. However, the casual relationship of VMS with these diseases and the exact underlying mechanism(s) have yet to be revealed. Further, we should ascribe importance to exploring these associations because of the effect of menopausal HRT on these chronic diseases as well as on VMS. Based on accumulating evidence, HRT for treatment of VMS might be a standard treatment for selected patients with VMS and an increased risk of these chronic diseases. On the contrary, HRT may have deteriorative effects in some patients with these diseases, such as heightened cardiovascular risk in specific populations; thus, further confirmative studies and prudent clinical application should be performed. Future research should aim to reveal the casual relationship of VMS with several chronic diseases, especially with

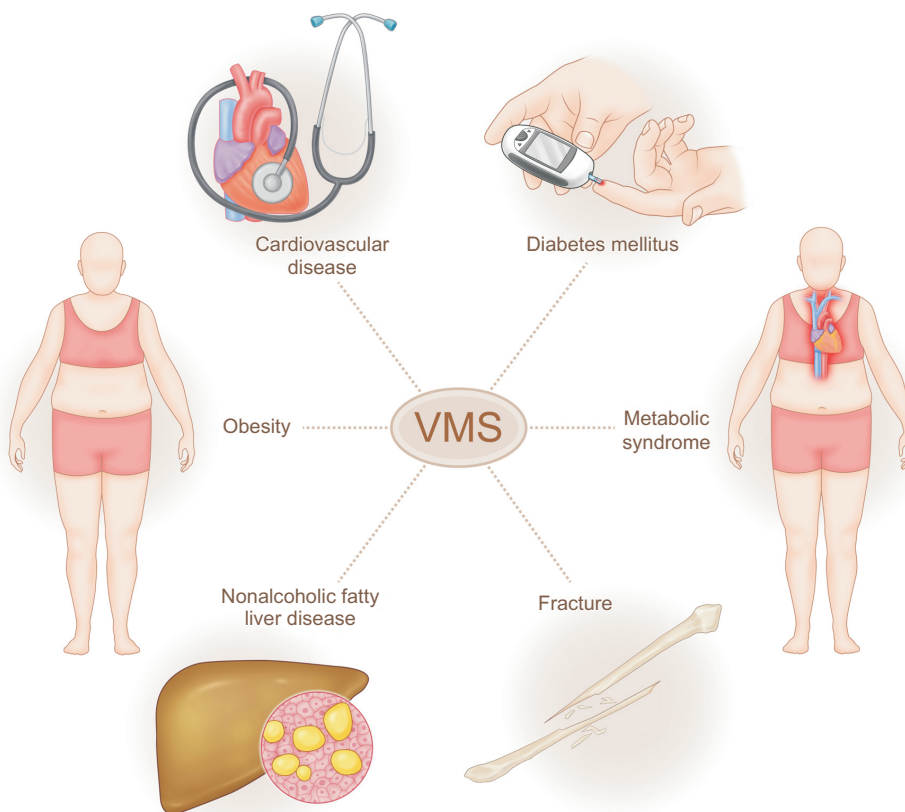


Fig. 2. Vasomotor symptoms (VMS) and chronic diseases in menopausal women. VMS are associated with increased risk of metabolic syndrome, insulin resistance, nonalcoholic fatty liver disease, osteoporosis, and cardiovascular diseases in menopausal women.

reliable objective measurement of VMS. Analysis of big data also might assist in identifying the relationship of VMS with various factors in a real-world setting. More attention must be paid to the significance and management of VMS in middle-aged and older women.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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