



Moderate to severe vasomotor symptoms are risk factors for non-alcoholic fatty liver disease in postmenopausal women



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ABSTRACT

Objective: To evaluate the association between vasomotor symptoms (VMS) and non-alcoholic fatty liver disease (NAFLD) in postmenopausal women.

Methods: This cross-sectional study included 1793 Korean postmenopausal women aged 45–65 years who attended a routine health check at a Korean institution from January 2010 to December 2012. Their scores on the Menopause Rating Scale were used to assess VMS. Moderate to severe VMS included ratings of moderate, severe, and very severe. NAFLD was diagnosed by abdominal ultrasound among those who indicated that their ethanol intake was less than 70 g/week.

Results: The mean age of these participants was 54.51 ± 4.74 years and the mean duration of menopause was 5.36 ± 4.41 years. A total of 602 (33.6%) women reported mild VMS while 435 (24.3%) reported moderate to severe VMS. The prevalence of NAFLD differed significantly according to the severity of VMS (none, 31.7%; mild, 34.9%; moderate to severe, 39.1%; $p = 0.037$). Levels of the liver enzymes alanine aminotransferase, alkaline phosphatase, and gamma-glutamyl transferase were significantly higher in women with moderate to severe VMS than in those without VMS. Logistic regression analysis revealed that moderate to severe VMS were significantly associated with the risk of NAFLD (OR: 1.50, 95% CI: 1.10–2.03) after adjusting for age, years since menopause, central obesity, alcohol use, smoking, exercise, and insulin resistance.

Conclusions: Moderate to severe VMS are associated with NAFLD and worse liver function profiles in otherwise healthy postmenopausal women. Further longitudinal studies are needed to investigate casual relationships and underlying mechanisms.

1. Introduction

Vasomotor symptoms (VMS) have received a great deal of attention due to their relationship with several impaired cardiometabolic conditions in postmenopausal women. VMS include hot flashes and night sweats. It is known that 50–75% of perimenopausal and postmenopausal women experience some degree of VMS during their lifetime [1,2]. Epidemiologic studies have indicated that VMS are associated with lower quality of life, abdominal obesity, impaired lipid profile, increased blood pressure, insulin resistance, subclinical atherosclerosis, vascular inflammation, and risk of cardiovascular disease [3–7]. Most of these conditions are associated with metabolic syndrome [8]. Despite the clinical importance of VMS, its physiologic mechanisms or associated metabolic conditions have not been fully elucidated yet.

Metabolic syndrome and insulin resistance often manifest in the liver as non-alcoholic fatty liver disease (NAFLD). NAFLD is a term used

to describe a spectrum of disorders characterized by excessive lipid accumulation in the liver, referred to as hepatic steatosis, with or without fibrotic changes and active inflammation in the liver parenchyma of patients who deny abusive alcohol consumption [9]. Although NAFLD may progress to advanced fibrosis, cirrhosis, and even liver cancer, most patients are asymptomatic until late stages of the disease [10]. Thus, it is clinically important to evaluate and screen for risk factors of NAFLD. Aging, obesity, and insulin resistance are well-known risk factors of NAFLD [11]. Concern about NAFLD is growing due to worldwide increase of obesity and diabetes. The incidence of NAFLD is higher in men compared to that in women during their reproductive years. However, postmenopausal women are at high risk for developing NAFLD [12,13]. Menopause and low estrogen levels are now believed to induce or aggravate NAFLD [14,15]. However, there are no prior studies examining the association between clinical symptoms of menopause and NAFLD.

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Significant relationships among VMS, insulin resistance, and metabolic syndrome in postmenopausal women have been established in previous studies [16]. Considering the close association between these conditions and NAFLD, we hypothesized that VMS might also be associated with NAFLD. Thus, the purpose of the present study was to investigate relationship between presence and severity of VMS and prevalence of NAFLD in otherwise healthy postmenopausal women.

2. Materials and methods

2.1. Subjects

This cross-sectional study began with 2457 Korean postmenopausal women aged 45–65 years who self-referred for a routine health check at Korea University Anam Hospital (Seoul, Korea) between January 2010 and December 2012. Postmenopausal status was defined by at least 12 consecutive months of amenorrhea without other medical cause. All women were interviewed and examined by an attending gynecologist. Written informed consent was obtained from all participants. Approval of this study was obtained from the Institutional Review Board of Korea University Medical Center.

Patients were excluded from this study for the following reasons: lack of information on menopausal symptoms, infection with viral hepatitis B or C (HBsAg or anti-HCV positive), hemochromatosis, current hormone use and taking any other drugs for the relief of VMS, current medication for diabetes mellitus or dyslipidemia, depressive mood disorder, overt thyroid disorder, history of hysterectomy or bilateral oophorectomy, history of chemotherapy or pelvic radiotherapy due to malignant disease, presence of cardiovascular disease such as prior myocardial infarction, angina, stroke, and peripheral arterial diseases, presence of chronic diseases such as renal failure, liver cirrhosis, and current infectious diseases, or alcohol intake greater than one bottle of soju (a Korean distilled liquor) or three bottles of beer (more than about 70 g of ethanol) per week. After exclusion, a total of 1793 women were eligible for this study (Fig. 1).

2.2. Anthropometric and laboratory measurements

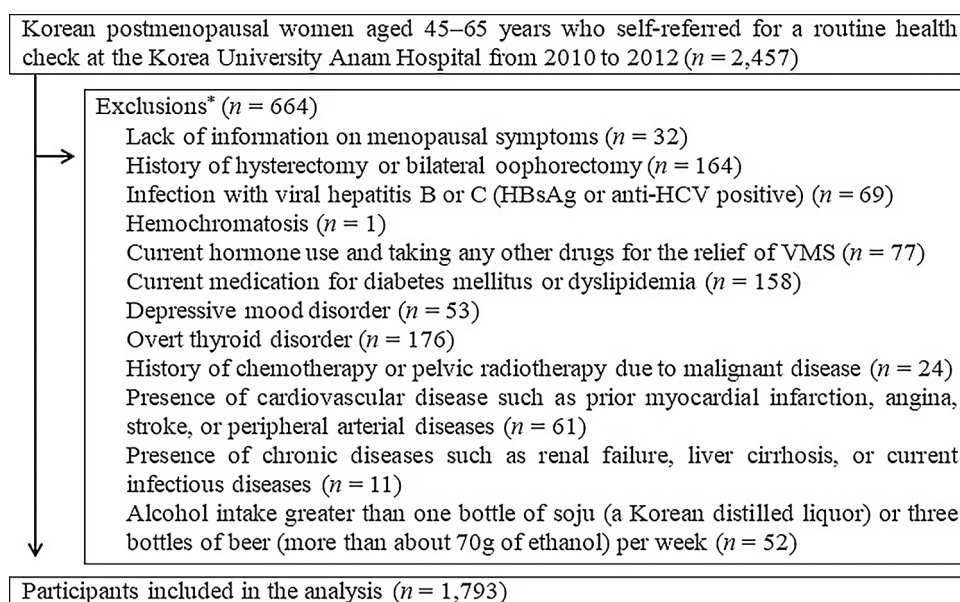
Height and body weight were measured for all women using a standard protocol. Body mass index (BMI, kg/m²) was calculated using

those results. Waist circumference was defined as the minimum distance around the torso between the costal margin and the iliac crest while participants were standing upright and breathing normally. Overweight/obesity was defined as BMI \geq 25.0 kg/m² while central (abdominal) obesity was defined as waist circumference \geq 85 cm. Blood pressure (BP) was measured using a standard mercury sphygmomanometer after participants were at a rest for at least 10 min.

Laboratory data were collected from all women by venous blood sampling at 9:00 AM after overnight fasting. Insulin levels were determined via radioimmunoassay using a commercially available kit (Biosource Europe S.A., Nivelles, Belgium). Homeostasis model assessment of insulin resistance index (HOMA-IR) was calculated using the following formula: fasting plasma glucose (mg/dL) \times fasting plasma insulin (IU/mL) / 405. Measurements of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), fasting glucose, total cholesterol, HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), triglycerides (TG), and C-reactive protein (CRP) were assessed via routine clinical chemistry methods. Among liver enzymes, AST and ALT are indicators of hepatocellular injury while GGT and ALP are mainly used as cholestasis markers, although GGT is more specific for biliary diseases compared to ALP [17].

2.3. Assessment of vasomotor symptoms

To assess the presence and severity of VMS in menopausal women, we used a questionnaire based on Menopause Rating Scale (MRS) that was developed and validated to measure the severity of menopause-related complaints [18]. Each of eleven questions included in that questionnaire was rated from zero (no complaint) to four (extremely severe symptoms) points depending on the perceived severity of complaints. From results of first MRS, a trichotomous variable was created for the absence of VMS, mild VMS, or moderate-to-severe VMS. The moderate-to-severe category was created due to the relatively small number of women with severe and very severe symptoms. Mild VMS was defined as an MRS score of one. Moderate-to-severe VMS was defined as an MRS score of two to four while a score of zero indicated the absence of VMS.



*Some participants met simultaneously two or more exclusion criteria.

Fig. 1. Flow diagram showing inclusion and exclusion of participants.

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