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Article

Low-Frequency Episodic Migraine with Aura and Associated Hypertension in Overweight Postmenopausal Women: Interplay of Serum Interleukin-6 and Vitamin D

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Abstract

Background and Objectives: Studies in hypertension (HTN), migraine (MIG) and HTN associated MIG (HMIG) in women present a link between vascular disorders and migraine. However, there are controversial findings yet for the important factors involved in overweight (OW) women with HTN and HMIG in postmenopause (PMP). Therefore, we planned to investigate the interactive role of body mass index (BMI) based serum levels of interleukin-6 (IL-6) and vitamin D (VitD) in PMP women with HTN, and low frequency episodic MIG and HMIG with aura. **Materials and Methods:** The subject groups of normal weight normotensives (NW-NTN), OW-NTN, NW-HTN, OW-HTN, NW-MIG, OW-MIG, NW-HMIG and OW-HMIG in PMP women (n:1008) were studied for investigating the BMI based variations and associations of IL-6 and VitD. Age range in each PMP women group (n:126) was 51-60 years. BMI range respectively in NW and OW participants was $\geq 18.5 - \leq 24.9$ and $\geq 25 - \leq 29.9$ kg/m². **Results:** Among groups variations indicated highly significant change in serum IL-6 and VitD. The post hoc Tukey Kramer test for HTN groups indicated significant increased VitD in OW-HTN compared to OW-NTN and NW-HTN, and significantly increased IL-6 in OW-HTN compared to OW-NTN and NW-HTN as well as OW-NTN compared to NW-NTN. Significant increased IL-6 was obtained in OW-MIG compared to NW-MIG and OW-HTN, NW-HMIG compared to NW-NTN, and OW-HMIG compared to OW-MIG, NW-HMIG and OW-NTN. The multiple linear regression indicated collective significant effect among BMI, IL-6, and VitD in OW-HTN, NW-MIG, OW-MIG, NW-HMIG and OW-HMIG. BMI and IL-6 presented significant inverse association with VitD in these groups. The remaining groups presented non-significant effect. **Conclusion:** Current study shows significant role of serum IL-6 and VitD in HTN and low-frequency episodic MIG and HMIG especially with OW status in PMP women. BMI based significant variation and negative association of IL-6 with vitamin D in HTN, and low-frequency episodic MIG and HMIG with aura in the present report provides evidence of the pathophysiological impact of IL-6 and vitamin D in HTN, and episodic MIG and HMIG.

Keywords: hypertension; low-frequency episodic migraine with aura; hypertension associated migraine; normal weight and overweight postmenopausal women; IL-6; vitamin D

Introduction

Hypertension (HTN) studies in women with migraine (MIG) and hypertension associated MIG (HMIG) presented a link between vascular/cardiovascular diseases (CVDs) and MIG [1], and increased CVDs were frequently noted associated to MIG with aura [2]. The MIG or the MIG headache, a major public health issue [3] presents high prevalence and is one of the main disabling neurological complications worldwide [4]. It manifests severe headaches that are more prevalent in women than men [5]. The overweight (OW) status and obesity are also common in postmenopause (PMP) in women with MIG [6].

Hypertension (HT) is one of the main health issues prevalent world-over and essentially requires to be investigated thoroughly by screening procedures, prevention measures, and treatment strategies with urgent and immediate attention [7]. Three generally accepted grades of HT for systolic blood pressure (SBP) and diastolic blood pressure (DBP) are: 140–159 and 90–99 (grade-1); 160–179 and 100–109 (grade-2); and ≥ 180 and ≥ 110 , though the lifestyle measures and treatment strategies do not correspond to any specific grade [8].

Collective effect of MIG and OW/ obesity in PMP women was revealed [6]. Other reports show relationship of blood pressure (BP) with body mass index (BMI) in NW-BMI and OW-BMI subjects [9], independent effects of OW/ obesity and HTN leading to vascular and CVDs disorders [10], effect of OW/ obesity causing HTN and effect of HTN causing OW/ obesity [9], influence of OW/ obesity in HTN, CVDs, and neurovascular/ neurological disorders [11], influence of HTN in OW and obese individuals [12], positive association of MIG and HTN [13], and several fold increase in the prevalence of HTN in MIG patients [14]. However, other studies [15,16] differ from the mentioned reports, e.g., no clear evidence of the exact direction manifesting association of OW/ obesity with MIG [16], inconsistent association of HTN and MIG [15], and no associations between HTN and MIG [17]. Involvement of HTN in MIG with or without aura is also not clearly known. It was revealed that risk of HTN increases in menopause in patients with MIG, but non-significant difference of the occurrence of HTN was noted in MIG patients with aura and in those without aura [18].

Controversial results have been documented for serum vitamin D (VitD) in PMP women with HTN, MIG and HMIG. Beneficial influence of VitD in PMP women with MIG [19], and favorable effects of VitD supplementation in patients with MIG [20] were documented. However, no significant relationship of low grade HTN with VitD in NW participants [21] was found. Non-significant association of general/ abdominal obesity with VitD in MIG patients [22], and conflicting findings for the association of VitD in PMP women [23] were obtained.

Increased cerebrospinal fluid (CSF) levels of interleukin-6 (IL-6) in HTN associated with headache and MIG attacks [24], and significant association of IL-6 and VitD with OW/ obesity and HTN in PMP women [25] were obtained. However, decreased level of IL-6 and its negative association with MIG in women with/without aura [26], and non-significant association of vasomotor activity and IL-6 [27] were also investigated. Furthermore, controversial relationship of serum IL-6 and VitD with OW/ obesity and HTN in PMP women [9] was documented.

It is generally viewed that lifestyle, eating behavior, adipocytokines, inflammatory/ anti-inflammatory biomarkers and other factors might influence the main pathophysiological factors involved in the underlying mechanism of a disease/ diseased process. These processes could be closely associated with vascular and neurovascular disorders including HTN, MIG and HMIG. However, there is no widely recognized evidence available yet of the mentioned factors in OW women in PMP for clarifying the involved mechanism.

Despite differing views and controversial findings, our pilot studies and the literature provided a guiding information to investigate the precise role of OW status and HTN in low-frequency episodic MIG with aura in PMP women. We reviewed the findings appearing in the relevant reports for

understanding and deciding for which specific biomarkers could be the promising factors for pathophysiological and therapeutic purposes. We hypothesized the possible involvement of a highly important anti-inflammatory biomarker-VitD that could partly be influenced by one of the major pro-inflammatory biomarkers- IL-6 in PMP women of OW status with HTN, MIG or HMIG.

To test and verify our proposed hypothesis, we planned to study the NW and OW women suffering from the low-frequency episodic MIG in PMP with aura and with/ without the risk of HTN. We focused on investigating the interactive change and association of serum IL-6 and VitD in PMP women of normal weight normotensive (NW-NTN), overweight normotensive (OW-NTN), normal weight hypertensive (NW-HTN), overweight hypertensive (OW-HTN), normal weight migraine (NW-MIG), overweight migraine (OW-MIG), normal weight migraine with hypertension (NW-HMIG), and overweight migraine with hypertension (OW-HMIG).

Materials and Methods

Participants and Study Design:

The total PMP women participants including controls in the present observational case control study were 1008. They were classified into eight groups. Each group comprised 126 participants. The age range in each PMP group was 51-60 years. Eight groups of participants in the present work comprised the NW-NTN, OW-NTN, NW-HTN, OW-HTN, NW-MIG, OW-MIG, NW-HMIG and OW-HMIG women. The BMI range respectively in NW and OW participants was $\geq 18.5 - \leq 24.9$ and $\geq 25 - \leq 29.9$ kg/m². The study was conducted during 15th January 2025 to 15th December 2025 at Umm Al-Qura University (UQU) and associated hospitals/main clinics in Makkah, Saudi Arabia, and the work was carried out considering the instructions and standard methods for human studies as recommended by UQU and Helsinki Declaration. The ethical approval was sanctioned by the ethical committee of the UQU Faculty of Medicine (the Approval Number: HAPO-02-K-012-2022-01-1069). Age and BMI matched subjects with HTN and MIG along with their corresponding controls were consulted. The sample size (n) was calculated prior to the commencement of research work by, $n = z^2 \cdot p \cdot (1-p) / e^2$ (z, p & e represent respectively the confidence level (α), proportion, and margin of error) [28]. Additionally, the sample size was verified by sample size calculator.

Assessments and Methods:

A Questionnaire was used for filling/recording the required information of the present and previous history of the patients and controls. For categorizing the participants into BMI-based NW and OW status, a standard local Saudi study was followed [29]. The BMI (kg/m²) levels were determined by dividing the body weight in kilograms (kgs) with the square of the body height in meters (m²) [29,30].

The familial records, and the record of current and past medication of the participants were collected. Those with a serious CVDs and any other complications except HTN, MIG and HMIG were not entertained. Anthropometric, clinical, and relevant laboratory information was collected. The participants in all eight groups of PMP women had a specified range of BP. Only those having grade-1 HTN were included in the present study. The range of the grade-1 HTN was considered: SBP/DBP as 140 to 159/ 90-99 mmHg [31]. The PMP participants having grade-2 HTNs (SBP/DBP: 160 to 179/100 to 109) and grade-3 HTNs (SBP/DBP: $\geq 180 / \geq 110$) [31] were not included in present study.

The PMP participants in the current study are those subjects who reached to the period of menopause, and PMP was designated by determining it retrospectively after women had gone 12 consecutive months without a period. All women included in the present study showed menopause up to 50 years of their age, and one year after that was considered as PMP, and the data of these participants was taken during 51-60 years of their age.

The MIG is generally classified into three types: common MIG or MIG without aura, classic MIG or MIG with aura, and chronic MIG. We consulted the participants having MIG with aura in the present study. The classic MIG or MIG with aura includes the sensory disturbances which generally

happen prior to or during MIG/ intense head-pain. Aura symptoms-most commonly visual disturbances develop and may last up to around an hour. The MIG participants with/ without HTN in the current study had low frequency episodic MIG (less than 10 migraine days in each month) with aura. The PMP women having MIG (with/ without HTN) but without aura, and the chronic MIG types were not included in the current study.

Obese and tobacco smoking participants were not included in the present study. The participants with anemia, type-2 diabetes mellitus (T2DM)/ type-1 diabetes mellitus (T1DM), or those subjects taking VitD, vitamin B or folic acid were not consulted. The participants having inflammatory, immune related, reproductive, renal, other vascular/ cardiovascular, neurovascular or any other complicated disorders were not considered for the present study. The PMP participants included were those women having HTN, and low frequency episodic MIG with/ without HTN, and controls.

Hematology analyzer-(Sysmex XN 100i (Sysmex Europe SE, Norderstedt, Germany) was employed for determining hemoglobin (Hb) levels. Serum IL-6, hepcidin (Hp) and VitD and Hp were determined respectively by Human IL-6 enzyme linked immunosorbent assay (ELISA) Kit, VitD ELISA kit following the manufacturer’s instructions (Euroimmun, Lubeck, Germany), and Human Hp ELISA Kit (MyBioSource, Inc. San Diego, CA, United States) employing the ELISA reader following the instructions of the manufacturer.

Data Analysis:

General statistical procedures [32] were followed for data analysis. Statistical-Package for Social Sciences (SPSS, vs 24.0) was incorporated for statistical analysis. Methods of descriptive statistics were employed for statistical analysis. The unpaired t-test was incorporated for two variable comparisons. Significant difference was considered as ≤ 0.05 . One-way analysis of variance (one-way ANOVA) and post hoc Tukey Kramer test provided the among groups comparisons.

Relationship for the dependent and independent variables and the goodness of fit were obtained employing multiple linear regression. Significant and non-significant predictors were found. The SPSS uses variables transformations, calculates the linear equation, R, R², adjusted R² (R²_{adj}), p-value, outliers that influence the Fisher-Pearson coefficient of skewness and the adjusted Fisher-Pearson coefficient of skewness. It represents regression, residual, and total degree of freedom (DF). After checking the residuals' normality assumption, it uses correlation matrices for multicollinearity, homoscedasticity assumption for equal variance in all levels of independent variable and priori power for minimum sample size, and the SPSS interprets the results. It then draws a histogram, a residuals Q-Q plot (Quantile-Quantile plot) for determining the errors or residuals, a tabular correlation matrix (Pearson), a residual x-plot-the diagnostic graph for residuals vs. predictor plot, and a graphical distribution chart. Excluding any predictor or running backward stepwise selection automatically is based upon the predictor's p-value. The backward stepwise technique is employed to produce an initial screening of the predictors till p-value threshold.

Results

Table 1 presents the BMI-based characteristics and variables among groups in PMP women participants with and without HTN. The Age (years) of the participants did not differ significantly (age range: 51-55 years). BMI (kg/m²) of NW subjects was in the range of 18.5-24.5 whereas it was 25-29.5 for OW subjects. The participants in the present study were thoroughly examined. Hb (g/dL) and Hp (ng/mL) were determined. The BMI-based variations and associations of IL-6 and VitD were determined in the present study for understanding their role in HTN, MIG and co-occurrence of HMIG. No significant variation in the age, Hb and Hp were found for HTN compared with NTN participants.

Serum VitD increased significantly in OW-HTN compared to OW-NTN and NW-HTN. IL-6 varied by its significantly increased serum levels in OW-HTN compared to OW-NTN and NW-HTN as well as OW-NTN compared to NW-NTN (Table 1).

Table 1. BMI-based characteristics and variables among groups in postmenopausal women participants with and without hypertension.

Variables	Normal-weight and overweight postmenopausal women with and without hypertension							
	NW-NTN vs. NW-HTN		OW-NTN vs. OW-HTN		NW-NTN vs. OW-NTN		NW-HTN vs. OW-HTN	
	NW-NTN	NW-HTN	OW-NTN	OW-HTN	NW-NTN	OW-NTN	NW-HTN	OW-HTN
Age (years)	55.64±2.91	55.67±2.89	55.71±2.84	55.71±2.87	55.64±2.91	55.71±2.84	55.67±2.89	55.71±2.87
BMI (kg/m ²)	21.05±2.11	21.08±2.07	27.20±1.69	27.20±1.60	21.05±2.11	27.20±1.60* ¹	21.08±2.07	27.20±1.60* ²
25(OH)D (ng/mL)	31.94±7.24	31.96±7.11	30.79±6.56	28.58±7.16* ³	31.94±7.24	30.79±6.56	31.96±7.11	28.58±7.16* ⁴
Hb (g/dL)	13.66±1.28	13.69±1.38	13.75±1.19	13.75±1.40	13.66±1.28	13.75±1.19	13.69±1.38	13.75±1.40
IL-6 (pg/ml)	7.86±7.36	9.50±6.90	9.80±7.11	14.15±8.37* ⁵	7.86±7.36	9.80±7.11* ⁶	9.50±6.90	14.15±8.37* ⁷
Hp (ng/mL)	8.59±3.87	8.60±3.98	8.26±4.24	8.47±4.34	8.59±3.87	8.26±4.24	8.60±3.98	8.47±4.34

NW-NTN: normal-weight normotensive, NW-HTN: normal weight hypertensive, OW-NTN: overweight normotensive, OW-HTN: overweight hypertensive, BMI: body mass index, Hb: haemoglobin, 25(OH)D: vitamin D (VitD), IL-6: interleukin-6, Hp: hepcidin, total number of participants in each group are 126, two-tailed p-value was used employing unpaired two-samples t-test, values are mean± standard deviation (SD), *¹: p<0.001 (OW-NTN vs. NW-NTN), *²: P<0.001 (OW-HTN vs. NW-HTN), *³: p 0.01 (OW-HTN vs. OW-NTN), *⁴: p<0.001 (OW-HTN vs. NW-HTN), *⁵: p<0.001 (OW-HTN vs. OW-NTN), *⁶: p 0.03 (OW-NTN vs. NW-NTN), *⁷: p<0.001(OW-HTN vs. NW-HTN), other comparisons did not show significant difference.

The BMI-based PMP groups showed significant increased IL-6 in OW-MIG compared to NW-MIG (Table 2). All other variables were found showing no significant differences in NW-MIG and OW-MIG patients compared to their respective normal controls.

Table 2. BMI-based characteristics and variables among groups in normotensive postmenopausal women participants with and without migraine.

Variables	Normal-weight and overweight normotensive postmenopausal women with and without migraine					
	NW-NTN vs. NW-MIG		OW-NTN vs. OW-MIG		NW-MIG vs. OW-MIG	
	NW-NTN	NW-MIG	OW-NTN	OW-MIG	NW-MIG	OW-MIG
Age (years)	55.64±2.91	55.67±2.87	55.71±2.84	55.68±2.81	55.67±2.87	55.68±2.81
BMI (kg/m ²)	21.05±2.10	21.08±2.08	27.20±1.60	27.20±1.61	21.08±2.08	27.20±1.61* ¹
25(OH)D (ng/mL)	31.94±7.24	31.08±0.63	30.79±6.56	29.93±6.32	31.08±7.02	29.93±6.32
Hb (g/dL)	13.66±1.28	13.64±1.39	13.75±1.19	13.70±1.40	13.64±1.39	13.70±1.40
IL-6 (pg/ml)	7.86±7.36	9.03±8.21	9.80±7.11	11.00±7.71	9.03±8.20	11.00±7.71* ²

Hp (ng/mL)	8.59±3.87	8.55±3.96	8.26±4.24	8.44±4.35	8.55±3.96	8.44±4.35
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NW-NTN: normal-weight normotensive, NW-MIG: normal weight migraine, OW-NTN: overweight normotensive, OW-MIG: overweight MIG, BMI: body mass index, Hb: haemoglobin, 25(OH)D: vitamin D (VitD), IL-6: interleukin-6, Hp: hepcidin, total number of participants in each group are 126, two-tailed p-value was used employing unpaired two-samples t-test, values are mean± standard deviation (SD), *1: p<0.001 (OW-MIG vs. NW-MIG), *2: P 0.05 (OW-MIG vs. NW-MIG), other comparisons did not show significant difference.

Table 3 describes the BMI-based characteristics and variables among groups in PMP women participants with and without HMIG. The comparisons present significant increased IL-6 and VitD levels in OW-HMIG compared to NW-HMIG as well as OW-NTN. IL-6 showed significant increased level in NW-HMIG compared to NW-NTN. Other variables were not found having significant variation in NW-HMIG, or OW-HMIG groups of patients.

Table 3. BMI-based characteristics and variables among groups in postmenopausal women participants with and without hypertension related migraine.

Variables	Normal-weight and overweight postmenopausal women with and without hypertension related migraine					
	NW-NTN vs. NW-HMIG		OW-NTN vs. OW-HMIG		NW-HMIG vs. OW-HMIG	
	NW-NTN	NW-HMIG	OW-NTN	OW-HMIG	NW-HMIG	OW-HMIG
Age (years)	55.64±2.91	55.67±2.87	55.67±2.80	55.67±2.84	55.67±2.87	55.67±2.84
BMI (kg/m²)	21.05±2.11	21.08±2.07	27.20±1.60	27.20±1.60	21.08±2.07	27.20±1.60 *1
25(OH)D (ng/mL)	31.94±7.24	30.67±7.10	30.79±6.56	27.51±6.98 *2	30.67±7.10	27.51±6.98 *3
Hb (g/dL)	13.67±1.28	13.63±1.36	13.75±1.19	13.75±1.34	13.63±1.36	13.75±1.34
IL-6 (pg/ml)	7.86±7.36	10.83±8.13 *4	9.80±7.11	15.53±9.14 *5	10.83±8.13	15.53±9.14 *6
Hp (ng/mL)	8.59±3.87	8.76±4.03	8.26±4.24	8.62±4.32	8.76±4.03	8.62±4.32

NW-NTN: normal-weight normotensive, NW-HMIG: normal weight hypertensive migraine, OW-NTN: overweight normotensive, OW-HMIG: overweight HMIG, BMI: body mass index, Hb: haemoglobin, 25(OH)D: vitamin D (VitD), IL-6: interleukin-6, Hp: hepcidin, total number of participants in each group are 126, two-tailed p-value was used employing unpaired two-samples t-test, values are mean± standard deviation (SD), *1: p<0.001 (OW-HMIG vs. NW-HMIG), *2: P<0.001 (OW-HMIG vs. OW-NTN), *3: p 0.001 (OW-HMG vs. NW-HMG), *4: p<0.003 (NW-HMIG vs. NW-NTN), *5: p<0.001 (OW-HMIG vs. OW-NTN), *6: p<0.001 (OW-HMIG vs. NW-HMIG), other comparisons did not show significant difference.

Table 4 describes the BMI-based characteristics and variables among groups in PMP women participants with HTN and with MIG. The comparisons present significant increased IL-6 in OW-MIG compared to OW-HTN. Other variables were not found having significant variation in NW-MIG, or OW-MIG compared to their respective groups of patients.

Table 4. BMI-based characteristics and variables among groups in postmenopausal women participants with hypertension and with migraine.

Variables	Normal-weight and overweight postmenopausal women with hypertension and with migraine
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	NW-HTN vs. NW-MIG		OW-HTN vs. OW-MIG	
	NW-HTN	NW-MIG	OW-HTN	OW-MIG
Age (years)	55.67±2.89	55.67±2.87	55.71±2.8	55.68±2.81
BMI (kg/m²)	21.08±2.07	21.08±2.08	27.20±1.60	27.20±1.61
25(OH)D (ng/mL)	31.96±7.11	31.08±0.63	28.58±7.16	29.93±6.32
Hb (g/dL)	13.69±1.38	13.64±1.39	13.75±1.40	13.70±1.40
IL-6 (pg/ml)	9.50±6.90	9.03±8.21	14.15±8.37	11.00±7.71 *1
Hp (ng/mL)	8.60±3.98	8.55±3.96	8.47±4.34	8.44±4.35

NW-NTN: normal-weight normotensive, NW-HTN: normal weight hypertensive, OW-NTN: overweight normotensive, OW-HTN: overweight hypertensive, BMI: body mass index, Hb: haemoglobin, 25(OH)D: vitamin D (VitD), IL-6: interleukin-6, Hp: hepcidin, total number of participants in each group are 126, two-tailed p-value was used employing unpaired two-samples t-test, values are mean± standard deviation (SD), *1: p<0.002 (OW-MIG vs. OW-HTN), other comparisons did not show significant difference.

Table 5 presents the BMI-based characteristics and variables among groups in PMP women participants with HTN and with HMIG. The comparisons did not present significant results for any variable.

Table 5. BMI-based characteristics and variables among groups in postmenopausal women participants with hypertension and with hypertension associated migraine.

Variables	Normal-weight and overweight postmenopausal women with hypertension and with hypertension associated migraine			
	NW-HTN vs. NW-HMIG		OW-HTN vs. OW-HMIG	
	NW-HTN	NW-HMIG	OW-HTN	OW-HMIG
Age (years)	55.67±2.89	55.67±2.87	55.71±2.8	55.67±2.84
BMI (kg/m²)	21.08±2.07	21.08±2.07	27.20±1.60	27.20±1.60
25(OH)D (ng/mL)	31.96±7.11	30.67±7.10	28.58±7.16	27.51±6.98
Hb (g/dL)	13.69±1.38	13.63±1.36	13.75±1.40	13.75±1.34
IL-6 (pg/ml)	9.50±6.90	10.83±8.13	14.15±8.37	15.53±9.14
Hp (ng/mL)	8.60±3.98	8.76±4.03	8.47±4.34	8.62±4.32

NW-NTN: normal-weight normotensive, NW-HTN: normal weight hypertensive, OW-NTN: overweight normotensive, OW-HTN: overweight hypertensive, BMI: body mass index, Hb: haemoglobin, 25(OH)D: vitamin D (VitD), IL-6: interleukin-6, Hp: hepcidin, total number of participants in each group are 126, two-tailed p-value was used employing unpaired two-samples t-test, values are mean± standard deviation (SD), no significant difference was obtained for group comparisons.

Table 6 describes the BMI-based characteristics and variables among groups in PMP women participants with MIG and with HMIG. The comparisons present significant increased IL-6 in OW-HMIG compared to OW-MIG. Other variables were not found having significant variation in NW-HMIG, or OW-HMIG compared to their respective groups of patients.

Table 6. BMI-based characteristics and variables among groups in postmenopausal women participants with normotensive migraine and with hypertension associated migraine.

Variables	Normal-weight and overweight postmenopausal women with normotensive migraine and with hypertension associated migraine			
	NW-MIG vs. NW-HMIG		OW-MIG vs. OW-HMIG	
	NW-MIG	NW-HMIG	OW-MIG	OW-HMIG
Age (years)	55.67±2.87	55.67±2.87	55.68±2.81	55.67±2.84
BMI (kg/m²)	21.08±2.08	21.08±2.07	27.20±1.61	27.20±1.60
25(OH)D (ng/mL)	31.08±0.63	30.67±7.10	29.93±6.32	27.51±6.98 * ¹
Hb (g/dL)	13.64±1.39	13.63±1.36	13.70±1.40	13.75±1.34
IL-6 (pg/ml)	9.03±8.21	10.83±8.13	11.00±7.71	15.53±9.14 * ²
Hp (ng/mL)	8.55±3.96	8.76±4.03	8.44±4.35	8.62±4.32

NW-NTN: normal-weight normotensive, NW-HTN: normal weight hypertensive, OW-NTN: overweight normotensive, OW-HTN: overweight hypertensive, BMI: body mass index, Hb: haemoglobin, 25(OH)D: vitamin D (VitD), IL-6: interleukin-6, Hp: hepcidin, total number of participants in each group are 126, two-tailed p-value was used employing unpaired two-samples t-test, values are mean± standard deviation (SD), *¹: p 0.004 (OW-HMIG vs. OW-MIG), *²: P<0.001 (OW-HMIG vs. OW-MIG), other comparisons did not show significant difference.

Among group variations determined by one way ANOVA and post hoc Tukey Kramer test indicated highly significant change in serum IL-6 and VitD (Table 7). Other variables did not indicate any significant change. The post hoc Tukey Cramer test indicated significant variations for serum IL-6 for: NW-HT & OW-HT, OW-NT & OW-HT, OW-NT & OW-HMIG, OW-HT & OW-MIG, OW-HT & NW-HMIG, OW-MIG & OW-HMIG, and NW-HMIG & OW-HMIG. It did not present any significant variations for age, Hp and Hb (Table 7).

The post hoc Tukey Cramer test presented significant variations for serum VitD for: NW-HT & OW-HT, NW-HT & OW-HMIG, OW-NT & OW-HMIG, NW-MIG & OW-HMIG and NW-HMIG & OW-HMIG (Table 7).

Table 7. Analysis of variance in BMI-based characteristics and variables in postmenopausal women participants with and without hypertension and migraine.

Participant variables		Normal control (NTN) (NW-NTN & OW-NTN)	Hypertension (HTN) (NW-HTN & OW-HTN)	Migraine (MIG) (NW-MIG & OW-MIG)	Hypertension and migraine (HMIG) (NW-HMIG & OW-HMIG)	Significance* (p-values)
Variables	BMI Status					
Age (years)	NW	55.64±2.91	55.67±2.89	55.67±2.87	55.67±2.87	>0.05
	OW	55.71±2.84	55.71±2.87	55.68±2.81	55.67±2.84	
BMI (kg/m2)	NW	21.05±2.11	21.08±2.07	21.08±2.08	21.08±2.07	<0.001
	OW	27.20 ±1.69	27.20±1.60	27.20±1.61	27.20±1.60	
IL-6 (pg/mL)	NW	7.86±7.36	9.50±6.90	9.03±8.21	10.83±8.13	<0.001
	OW	9.80±7.11	14.15±8.37	11.00±7.71	15.53±9.14	

Hp (ng/mL)	NW	8.59±3.87	8.60±3.98	8.55±3.96	8.76±4.03	0.99
	OW	8.26±4.24	8.47±4.34	8.44±4.35	8.62±4.32	
Hb (g/dL)	NW	13.66±1.28	13.69±1.38	13.64±1.39	13.63±1.36	0.99
	OW	13.75±1.19	13.75±1.40	13.70±1.40	13.75±1.34	
VitD	NW	31.94±7.24	31.96±7.11	31.08±0.63	30.67±7.10	<0.001
	OW	30.79±6.56	28.58±7.16	29.93±6.32	30.67±7.10	

NW-NTN: normal-weight normotensive, OW-NTN: over-weight normotensive, NW-HTN: normal weight hypertensive, OW-HTN: over-weight hypertensive, MIG: migraine, NW-MIG: normal weight migraine, OW-MIG: over-weight migraine, HMIG: hypertensive migraine, NW-HMIG: normal weight hypertensive migraine, OW-HMIG: overweight hypertensive migraine, BMI: body mass index, Hb: haemoglobin, 25(OH)D: vitamin D (VitD), IL-6: interleukin-6, Hp: hepcidin, total number of participants in each group are 126, , values are mean± standard deviation (SD), p-values for one-way ANOVA (one-way analysis of variance), statistical analysis was carried out by using “Statistical Package for Social-Sciences” version 24.0 for Window (SPSS, Ver 24.0), *: One-way analysis of variance (ANOVA).

For NW-NTM, the multiple linear regression presented weak cumulative nonsignificant effect between age, BMI, IL-6, Hp, Hb and Vitamin D ($F(1, 124) = 1.5, p = 0.222, R^2 = 0.01, R^2_{adj} = 0$) (Table 8). The predictors show a little variance of dependent variable. For multiple linear regression for NW-HTN, a weak cumulative non-significant effect was obtained between age, BMI, IL-6, Hp, Hb, and Vitamin D, ($F(1, 124) = 1.4, p = 0.238, R^2 = 0.01, R^2_{adj} = 0$) (Table 8). For OW-NTN, weak cumulative nonsignificant effect in multiple regression was obtained between age, BMI, IL-6, Hp, Hb and Vitamin D, ($F(1, 124) = 0.74, p = 0.393, R^2 = 0.01, R^2_{adj} = 0$) (Table 8).

Table 8. Analysis of correlation by multiple linear regression for all variables in postmenopausal women with normotension, hypertensive, migraine and hypertension associated migraine.

Subject groups	Correlation by multiple linear regression for age, BMI, IL-6, Hp, Hb and VitD in postmenopausal women with normotension, hypertension, migraine and hypertension associated migraine			
	F	R ²	R ² _{adj}	p
NW-NTN	1.50	0.01	0.00	0.22
NW-HTN	1.40	0.01	0.00	0.24
OW-NTN	0.74	0.01	0.00	0.39
OW-HTN	25.65	0.39	0.37	<0.001
NW-MIG	6.00	0.09	0.07	0.003
OW-MIG	5.97	0.09	0.07	0.003
NW-HMIG	8.72	0.12	0.11	<0.001
OW-HMIG	36.69	0.47	0.46	<0.001

NW: normal weight, OW: overweight, NTN: normotensive, HTN: hypertensive, MIG: migraine, HMIG: hypertensive migraine, F: Fisher's F or F-statistic (or F-value), R²: coefficient of determination, R²_{adj}: R² adjusted, multiple linear regression was employed, statistical analysis was done by applying the Statistical Package for Social Sciences (SPSS), version 24.0 for Windows.

The results for OW-HTN obtained from the multiple regression show that there was a strong collective significant effect between the IL-6, BMI, age, Hp, Hb, and Vitamin D, ($F(3, 122) = 25.65, p < .001, R^2 = 0.39, R^2_{adj} = 0.37$) (Table 8). Individual predictors were examined further and indicated that IL-6 ($t = -3.665, p < .001$), BMI ($t = 1.983, p = .050$) and age ($t = -2.698, p = .008$) were significant predictors in the model.

The analysis of multiple regression for NW-MIG shows that a collective significant effect was obtained between age, BMI, IL-6, Hp, Hb, and VitD, ($F(2, 123) = 6, p = 0.003, R^2 = 0.09, R^2_{adj} = 0.07$) (Table 8). The individual predictors were examined further and indicated that IL-6 ($t = -3.051, p = 0.003$) and BMI ($t = 2.562, p = 0.012$) were significant predictors in the model. The goodness of fit accompanied the overall p value $< \alpha$ (0.05). The results for OW-MIG showed that the multiple regression indicated a collective significant effect between the age, BMI, IL-6, Hp, Hb, and VitD, ($F(2, 123) = 5.97, p = 0.003, R^2 = 0.09, R^2_{adj} = 0.07$) (Table 8). The individual predictors were examined further and indicated that IL-6 ($t = -2.985, p = 0.003$) and BMI ($t = 2.528, p = .013$) were significant predictors. The goodness of fit accompanied the overall p value $< \alpha$ (0.05).

The multiple regression analysis for NW-HMIG indicated a collective significant effect between age, BMI, IL-6, Hp, Hb, and VitD, ($F(2, 123) = 8.72, p < .001, R^2 = 0.12, R^2_{adj} = 0.11$) (Table 8). The individual predictors were examined further and indicated that IL-6 ($t = -3.497, p < .001$) and BMI ($t = 2.786, p = .006$) were significant predictors. Analysis of the multiple linear regression for OW-HMIG indicated that there was a strong collective significant effect between the age, BMI, IL-6, Hp, Hb, and VitD, ($F(3, 122) = 36.69, p < .001, R^2 = 0.47, R^2_{adj} = 0.46$) (Table 8). The goodness of fit accompanied the overall p value $< \alpha$ (0.05). The individual predictors were examined further and indicated that IL-6 ($t = -5.694, p < .001$) and BMI ($t = 3.731, p < .001$) and age ($t = -2.663, p = .009$) were significant predictors.

Table 9 presents the results of the multiple regression for only BMI, IL-6, and vitamin D in PMP women with NTN, HTN, MIG and HMIG. This second set of multiple regression clarified the associations among three important predictors.

Table 9. Analysis of correlation by multiple linear regression for BMI, IL-6, and vitamin D in postmenopausal women with normotension, hypertensive, migraine and hypertension associated migraine.

Subject groups	Correlation by multiple linear regression for BMI, IL-6 and VitD in postmenopausal women with normotension, hypertension, migraine and hypertension associated migraine			
	F	R ²	R ² _{adj}	p
NW-NTN	1.50	0.01	0.00	0.22
NW-HTN	1.40	0.01	0.00	0.24
OW-NTN	1.72	0.01	0.01	0.19
OW-HTN	61.30	0.33	0.33	<0.001
NW-MIG	5.19	0.04	0.03	0.024
OW-MIG	5.31	0.04	0.03	0.023
NW-HMIG	9.17	0.07	0.06	0.003
OW-HMIG	76.54	0.38	0.38	<0.001

NW: normal weight, OW: overweight, NTN: normotensive, HTN: hypertensive, MIG: migraine, HMIG: hypertensive migraine, BMI: body mass index, VitD: vitamin D, IL-6: interleukin-6, F: Fisher's F or F-statistic (or F-value), R²: coefficient of determination, R²_{adj}: R² adjusted, multiple linear regression was employed, statistical analysis was done by applying the Statistical Package for Social Sciences (SPSS), version 24.0 for Windows.

Results of the multiple linear regression for NW-NTN indicated that there was a very weak collective non-significant effect between the BMI, IL-6, and VitD, ($F(1, 124) = 1.5, p = 0.22, R^2 = 0.01, R^2_{adj} = 0$) (Table 9). Results of the multiple linear regression for NW-HTN indicated that there was a very weak collective non-significant effect between the BMI, IL-6, and VitD, ($F(1, 124) = 1.4, p = 0.24, R^2 = 0.01, R^2_{adj} = 0$) (Table 9). Results of the multiple linear regression for OW-NTN indicated that there was a very weak collective non-significant effect between the BMI, IL-6, and VitD, ($F(1, 124) = 1.72, p = .192, R^2 = 0.01, R^2_{adj} = 0.01$) (Table 9).

Results of the multiple linear regression for OW-HTN indicated that there was a moderate collective significant effect between the BMI, IL-6, and VitD, ($F(1, 124) = 61.3, p < .001, R^2 = 0.33, R^2_{adj} = 0.33$) (Table 9). Results of the multiple linear regression for NW-MIG indicated that there was a collective significant effect between the BMI, IL-6, and VitD, ($F(1, 124) = 5.19, p = .024, R^2 = 0.04, R^2_{adj} = 0.03$) (Table 9). Results of the multiple linear regression for OW-MIG indicated that there was a collective significant effect between the BMI, IL-6, and VitD, ($F(1, 124) = 5.31, p = .023, R^2 = 0.04, R^2_{adj} = 0.03$) (Table 9). Results of the multiple linear regression for NW-HMIG indicated that there was a collective significant effect between the BMI, IL-6, and VitD, ($F(1, 124) = 9.17, p = .003, R^2 = 0.07, R^2_{adj} = 0.06$) (Table 9). Results of the multiple linear regression for OW-HMIG indicated that there was a strong collective significant effect between the BMI, IL-6, and VitD, ($F(1, 124) = 76.45, p < .001, R^2 = 0.38, R^2_{adj} = 0.38$) (Table 9). p-value is $< \alpha (0.05)$.

Discussion

The among groups variations indicated highly significant change in serum IL-6 and VitD in the present study. Hypertension group of overweight postmenopausal women in the present study indicated significant increased serum VitD in OW-HTN compared to OW-NTN and NW-HTN, and significantly increased IL-6 in OW-HTN compared to OW-NTN and NW-HTN as well as OW-NTN compared to NW-NTN. The migraine and hypertension associated migraine groups show significant increased IL-6 in OW-MIG compared to NW-MIG and OW-HTN, NW-HMIG compared to NW-NTN, and OW-HMIG compared to OW-MIG, NW-HMIG and OW-NTN. Among groups the multiple linear regression indicated collective significant effect among BMI, IL-6, and VitD in OW-HTN, NW-MIG, OW-MIG, NW-HMIG and OW-HMIG. BMI and IL-6 presented significant inverse association with VitD in these groups. Other groups presented non-significant effect.

Our current study provides evidence for the relationship of BMI with migraine in PMP women. Both the migraine and obesity/ overweightness are prevalent conditions with high financial burden and socioeconomic hardship in PMP women [6]. Migraine prevalence is more in women [33] with evident clinical characteristics in premenopause, menopause and PMP [34,35]. It was noted significantly higher in prevalence in PMP women compared to premenopausal women, and association between obesity/ overweight status and migraine and vice versa exists [6]. It exhibits severe headache and has two to three times more prevalence in females than in males [5,36]. This disparity is most significant during the reproductive age, and peaking in later years [5,37,38]. Migraine patterns in PMP were compared and it was suggested for further studies on large scale to better understand the related burden in PMP considering the migraine characteristics and management [39].

The present investigation presents association of OW status with HTN and HMIG. Several reports explain this association. Increased BMI may appear in response to HT [40]. A large population of different age range of obese subjects had HTN than a smaller number of NW people with HTN [41]. Gradually increasing BMI revealed progressive increase in HTN in public [11] even in late life [42]. An association for BP and BMI was revealed in both NW-BMI and OW-BMI individuals [43].

It was investigated that the body weight and HTN associate significantly with each other [9]. The OW status and HTN were found independent risk factors progressing to CVD [10]. Various reports provide convincing information about the significant role of OW-BMI and obesity related BMI (O-BMI) in the development and gradual progression to HTN and the occurrence of HTN leading to increase in BW and hence BMI. [9,43,44]. Regardless of the mentioned studies, differing

results and contradictory findings were also noted mainly due to differing criteria employed for collecting/obtaining and studying the data of obese and OW subjects with/ without HTN [43,44]. Our current study provides valuable information and suggests decreasing the body weight for better health strategy. An interactive influence between HTN and OW-BMI or HTN and O-BMI emphasizes to implement a combined type of management for both HTN and increased BMI even for non-HTN subjects with elevated BMI [45]. As a precautionary measure, it is helpful decreasing the body weight for future possibility of the risk of having HTN in subjects who do not have yet the obesity or OW status [31].

Obesity, HTN and other vascular diseases/CVDs and metabolic disorders are more prevalent in PMP women than men and these disorders appear in interaction more frequently in women than men [46]. The increased prevalence in women may stem from the fact that women typically have small sized coronary vessels, which can lead to disordered vasodilator reaction in the microvasculature and increased aortas stiffness. Consequently, a better insight and understanding of sex-specific biological differences are essentially required to be explored for deciding the efficacious management of HTN, vasculopathies and other CVDs in women.

The present study found a firm positive association between MIG and HTN that is evident in other studies as well [13,47]. A report conducted with follow-up for five years found 1.4-fold more risk of developing HTN [14]. However, some of the other reports that documented inconsistent results [15,48], no associations or negative association between HTN and MIG [17,49–51] could be due to the criteria for defining the various measurements and selecting the participants or methodological differences. We tried to conduct highly well controlled study following the required criteria. Hence, the results obtained in this study are further helpful for unravelling the influence of HTN in patients with MIG and vice versa.

It was revealed that the age, BMI, and PMP/menopausal status, presented both positive and negative associations with the history of MIG, HTN, menopausal syndrome and other metabolic disorders [52]. We noticed that the data [52] was categorized in a different way compared to ours, and the population of the participants is also different. The women participants in the current study in PMP presented the influence of hypertension on MIG with aura and vice versa. It was investigated that MIG was found associated with an increased risk of HTN in menopausal women, though no significant difference was found for migraine with or without aura [18]. However, we could not find comparison for the association of HTN in MIG women without aura since we collected only the data of MIG/ HMIG women with aura.

The OW-BMI and O-BMI are considered as the influencing factors contributing to the occurrence of HT, CVDs, neurological/ neurovascular disorders, diabetes mellitus (DM) and other chronic diseases [18]. The shift of NW-BMI to OW-BMI and O-BMI status steadily or speedily in public is a highly serious and alarming situation [53] causing CVDs. The BP increases more often in obese subjects compared to nonobese subjects, whereas change in lifestyle reduces the level of BP in obese and OW subjects [12].

The present report suggests the potential role of IL-6 in MIG. It was evident in a report that women participants having MIG showed increased levels of IL-6, and other pro-inflammatory cytokines as compared to control participants [54]. Furthermore, serum IL-6 correlated positively with the number of MIG headache days [55]. An experimental study showing increase in plasma IL-6 levels in stressed mice, with more pronounced increase in female mice predicted the involvement of IL-6 and other pro-inflammatory cytokines as well in the mechanisms supporting to the MIG pain [33]. Various cytokines including IL-6 are implied in the pathophysiology of MIG/MIG headaches via association between MIG and inflammation, immune dysfunctions, obesity, insulin resistance, atherosclerosis, HTN, CVDs and other dysfunctions [56].

Obesity in MIG can be treated effectively by bariatric surgery as a therapeutic alternate for considerable weight loss arising from decrease in systemic inflammation along with other factors [4]. It was revealed that magnitude of MIG headache improvement correlated well with the weight loss and under the influence of decrease in IL-6 and other proinflammatory cytokines. Related to the link

between obesity and MIG, it was found that obesity potentiates transient receptor potential ankyrin-1 (TRPA-1) associated trigemino-vascular reaction, and elevates the pro-inflammatory cytokine IL-6, and increased susceptibility occurs in obese subjects after chemical exposure to trigeminal nociceptors [57]. Obesity induced by long term administration of high-fat, high-sucrose (HFHS) in experimental animals caused increased levels of IL-6 and other proinflammatory cytokines, sensitizing the trigemino-vascular processes, and causing alterations in transient receptor potential vanilloid 1 (TRPV1) associated vascular processes serving as pathophysiological mechanism associated with the increased susceptibility of headache [57]. The vasomotor manifestations appearing during menopause transition are frequently reported as due to inflammatory disbalances. Obesity is considered as a risk factor for the change of episodic MIG to chronic MIG and IL-6 and other pro-inflammatory cytokines serve as neurogenic inflammatory factors producing MIG in patients with obesity [58].

Our study shows that IL-6 has dual pathophysiological role both in HTN and MIG. It is confirmed in a study that the patients with headache mainly from intracranial HTN and intractable and nonspecific forms of MIG presented increased levels of IL-6 in CSF [24]. The antiviral tests were carried out for determining the efficacy of *Elaeocarpus sylvestris ellipticus* (ESE) for varicella zoster virus (VZV). The ESE is a traditional oriental medication for pain, MIG, HTN, obesity and several other disorders. It was found that ESE decreased the pain response and inhibited the phosphorylation and the expression of IL-6 and several other anti-inflammatory cytokines leading to inhibitory action on pain and inflammation [59].

A firm change in the serum levels of VitD and association of vitamin D with MIG was found in the present work. A previous report provided evidence that VitD administration showed therapeutic efficacy in patients with MIG [20]. Furthermore, significant difference was obtained in VitD supplemented exercise training group compared to non-training control group for the menopausal symptoms including MIG in early PMP women [19].

The MIG, HTN, OW/obesity, and HTN and OW/ obesity associated MIG all show the efficacious role of vitamin D. A trial showed beneficial effects of VitD supplementation for three months on MIG [60]. Significantly greater decrease in the frequency and severity of MIG was obtained. Studies in a trial comprising adult patients having migraine revealed that supplementation of VitD improved the migraine index (MI), and nitric oxide (NO) serum levels [60]. Migraineurs showed higher association with HTN, obesity, VitD deficiency and a variety of other factors [61].

Interactive activity of VitD and IL-6 was shown in PMP women with HTN and MIG [62]. Another report indicates BMI based association of VitD insufficiency influencing serum IL-6 [63]. Relevant studies provide evidence for our findings for patients with HTN [64,65] and MIG [66,67]. Studies conducted in patients with DM, HTN and CVDs elucidated an association of VitD receptor (VDR) expression and IL-6 [64]. It was suggested that there exists a direct association between VitD and IL-6 in HTN women, though further studies are required in view of inconsistent results [65].

The IL-6 and other inflammatory mediators in interaction with a variety of dietary components including VitD were found important in weight loss dietary plans for OW and obese MIG patients [66]. It was revealed that VitD pertains anti-inflammatory effects and is helpful for improving the MIG headaches especially for protecting against inflammation in MIG patients [67]. They found that VitD supplementation helped decreasing IL-6 and other inflammatory responses in patients with episodic MIG [67]. This report is highly related for providing evidence for our current findings.

There are several merits and demerits of the present investigation. The merits in the current study are that it is highly well controlled with respect to age of the PMP participants, range of the period after menopause, their BMI, BP, HTN of grade-1, MIG of a highly specific type (low-frequency episodic MIG), and non-anemic/ nonobese/ nonsmoking status of the participants. Despite the merits of having well-controlled study, the mentioned criteria could be considered as having demerits or limitations, since comprehensive studies can be conducted by collecting the data of a): wide age range, b): comparative assessment of perimenopause (premenopause, menopause and PMP), c): wide range of BMI, and BP d): higher grades of HTN, e): MIG patients of various types-chronic and those

that are without aura, f): obese PMP women g): anemic PMP, h): MIG of moderate and high frequency, and i): MIG/ HMIG with other comorbidities. Furthermore, there is an urgent need of studying other inflammatory/ anti-inflammatory biomarkers and other variables of pathophysiological significance as well beside the interactive role of IL-6 and VitD with NW-BMI, OW-BMI and O-BMI status and central obesity. Hopefully, further studies would provide the opportunity to link the present findings with other promising future studies for having a better and comprehensive insight about the underlying mechanism in MIG with/ without HTN, and better management of OW/ obese PMP women patients having MIG with/ without HTN. It is expected that interlinking the existing and future findings would unravel a well-accepted mechanism of the development and progression of HTN/ MIG/ HMIG and their management based on comprehensive pathophysiological insights.

Conclusions

Current study shows significant role of serum IL-6 and vitD in HTN and low-frequency episodic MIG and HMIG especially with OW status in PMP women. BMI based significant variation and negative association of IL-6 with vitamin D in HTN, and low-frequency episodic MIG and HMIG with aura in the present report provide evidence of the pathophysiological impact of IL-6 and vitamin D in HTN, and episodic MIG and HMIG.

Abbreviations

The following abbreviations are used in this manuscript:

ANOVA	Analysis of variance
BMI	Body mass index
BP	Blood pressure
DM	Diabetes mellitus
ESE	Elaeocarpus sylvestris ellipticus
R	Correlation coefficient
R ²	Coefficient of determination
R ² _{adj}	Adjusted coefficient of determination
CSF	Cerebrospinal fluid
CVDs	Cardiovascular diseases
DBP	Diastolic blood pressure
ELISA	Enzyme linked immunosorbent assay
Hb	Hemoglobin
HFHS	High-fat, high-sucrose
Hp	Hepcidin
HTN	Hypertension
HMIG	Hypertension associated migraine
IL-6	Interleukin-6
MI	Migraine index
MIG	Migraine
n	Sample size
NO	Nitric oxide
NTN	Normotensive
NW	Normal weight
NW-BMI	Normal weight body weight index
NW-HMIG	Normal weight migraine with hypertension
NW-HTN	Normal weight hypertensive
NW-MIG	Normal weight migraine
NW-NTN	Normal weight normotensive
O-BMI	Obesity related BMI
25(OH)D	Vitamin D (VitD)
OW	Overweight
OW-BMI	Overweight body mass index

OW-HMIG	Overweight migraine with hypertension
OW-HTN	Overweight hypertensive
OW-MIG	Overweight migraine
OW-NTN	Overweight normotensive
PMP	Postmenopause/ postmenopausal
Q-Q plot	Quantile-Quantile plot
SBP	Systolic blood pressure
SPSS	Statistical-Package for Social Sciences
T1-DM	Type-1 diabetes mellitus
T2-DM	Type-2 diabetes mellitus
UQU	Umm Al-Qura University
VDR	Vitamin D receptor (VitD receptor)
VitD	Vitamin D
VZV	Varicella zoster virus

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References

1. Sacco, S.; Ricci, S.; Carolei, A. Migraine and vascular diseases: a review of the evidence and potential implications for management. *Cephalalgia* **2012**, *32*, 785-795.
2. Kurth, T.; Winte,r A.C.; Eliassen, A.H.; Dushkes, R.; Mukamal, K.J.; Rimm, E.B.; Willett, W.C.; Manson, J.E.; Rexrode, K.M. Migraine and risk of cardiovascular disease in women: prospective cohort study. *BMJ* **2016**, *353*, i2610. Erratum in: *BMJ* **2016**, *353*, i3411.
3. Tirani, S.A.; Khorvash, F.; Saneei, P.; Moradmand, Z.; Askari, G. Effects of probiotic and vitamin D co-supplementation on clinical symptoms, mental health, and inflammation in adult patients with migraine headache: a randomized, triple-blinded, placebo-controlled trial. *BMC* **2024**, *22*, 457.
4. Mahran, M.; Al-Asadi, O.; Sobh, R.; Salloum, D.; Aljaafreh, A. Effect of Bariatric Surgery on Migraine Headache: A Systematic Review and Meta-Analysis. *Cureus* **2025**, *17*, e97294.
5. Faubion, S.S.; Batur, P.; Calhoun, A.H. Migraine Throughout the Female Reproductive Life Cycle. *Mayo Clin. Proc.* **2018**, *93*, 639-645.
6. Saffari, T.M.; Kavanagh, K.; Ormseth, B.; Palettas, M.; Janis, J.E. Severe obesity is associated with increased migraine severity and frequency: A retrospective cohort study. *J. Clin. Neurosci.* **2023**, *115*, 8-13.
7. Kearney, P.M.; Whelton, M.; Reynolds, K.; Muntner, P.; Whelton, P.K.; He, J. Global burden of hypertension: analysis of worldwide data. *Lancet* **2005**, *365*, 217-223.
8. Williams, B.; Mancia, G.; Spiering, W.; Agabiti Rosei, E.; Azizi, M.; Burnier, M.; Clement, D.L.; Coca, A.; de Simone, G.; Dominiczak, A.; et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur. Heart J.* **2018**, *39*, 3021-3104.
9. Fantin, F.; Giani, A.; Zoico, E.; Rossi, A.P.; Mazzali, G.; Zamboni, M. Weight Loss and Hypertension in Obese Subjects. *Nutrients* **2019**, *11*, 1667.

10. Zhu, L.; Fang, Z.; Jin, Y.; Chang, W.; Huang, M.; Chen, Y.; Yao, Y. Circulating ERBB3 levels are inversely associated with the risk of overweight-related hypertension: a cross-sectional study. *BMC Endocr. Disord.* **2021**, *21*, 130.
11. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19.1 million participants. *Lancet* **2017**, *389*, 37-55. Erratum in: *Lancet* **2020**, *396*, 886.
12. Higashino, R.; Miyaki, A.; Kumagai, H.; Choi, Y.; Akazawa, N.; Ra, S.G.; Tanabe, Y.; Eto, M.; So, R.; Tanaka, K.; et al. Effects of lifestyle modification on central blood pressure in overweight and obese men. *Blood Press. Monit.* **2013**, *18*, 311-315.
13. Gardener, H.; Monteith, T.; Rundek, T.; Wright, C.B.; Elkind, M.S.; Sacco, R.L. Hypertension and Migraine in the Northern Manhattan Study. *Ethn. Dis.* **2016**, *26*, 323-330.
14. Entonen, A.H.; Suominen, S.B.; Korkeila, K.; Mäntyselkä, P.T.; Sillanmäki, L.H.; Ojanlatva, A.; Rautava, P.T.; Koskenvuo, M.J. Migraine predicts hypertension—a cohort study of the Finnish working-age population. *Eur. J. Public Health* **2014**, *24*, 244-248.
15. Sacco, S.; Pistoia, F.; Degan, D.; Carolei, A. Conventional vascular risk factors: their role in the association between migraine and cardiovascular diseases. *Cephalalgia* **2015**, *35*, 146-164.
16. Jahromi, S.R.; Martami, F.; Morad Soltani, K.; Togha, M. Migraine and obesity: what is the real direction of their association? *Expert Rev. Neurother.* **2023**, *23*, 75-84.
17. Winsvold, B.S.; Hagen, K.; Aamodt, A.H.; Stovner, L.J.; Holmen, J.; Zwart, J.A. Headache, migraine and cardiovascular risk factors: the HUNT study. *Eur. J. Neurol.* **2011**, *18*, 504-511.
18. MacDonald, C.J.; El Fatouhi, D.; Madika, A.L.; Fagherazzi, G.; Kurth, T.; Severi, G.; Boutron-Ruault, M. Association of Migraine With Incident Hypertension After Menopause: A Longitudinal Cohort Study. *Neurology* **2021**, *97*, e34-e41.
19. Kemmler, W.; von Stengel, S.; Weineck, J.; Lauber, D.; Kalender, W.; Engelke, K. Exercise effects on menopausal risk factors of early postmenopausal women: 3-yr Erlangen fitness osteoporosis prevention study results. *Med. Sci. Sports Exerc.* **2005**, *37*, 194-203.
20. Thys-Jacobs, S. Alleviation of migraines with therapeutic vitamin D and calcium. *Headache*, **1994**, *34*, 590-592.
21. Baniasad, A.; Mokhtari Ardekan, A.; Najafzadeh, M.J.; Mousavi Mehdiabadi, F. The relationship between vitamin D and short-term blood pressure variability. *Blood Press. Monit.* **2023**, *28*, 193-198.
22. Khorvash, F.; Mottaghi, T.; Askari, G.; Maracy, M.R.; Ghiasvand, R.; Maghsoudi, Z.; Iraj, B.; Nejad, M.A. The association between serum vitamin d levels with general and abdominal obesity among patients with migraine. *Int. J. Prev. Med.* **2013**, *4*, S313-317.
23. Hao, L.; Lu, A.; Gao, H.; Niu, J.; Prabakar, K.; Seraj, S.S.; Pan, Y. The Effects of Vitamin D on Markers of Glucose and Obesity in Postmenopausal Women: A Meta-analysis of Randomized Controlled Trials. *Clin. Ther.* **2023**, *45*, 913-920.
24. Frago-Loyo, H.; Atisha-Fregoso, Y.; Llorente, L.; Sánchez-Guerrero, J. Inflammatory profile in cerebrospinal fluid of patients with headache as a manifestation of neuropsychiatric systemic lupus erythematosus. *Rheumatology (Oxford)* **2013**, *52*, 2218-2222.
25. WHO CVD Risk Chart Working Group. World Health Organization cardiovascular disease risk charts: revised models to estimate risk in 21 global regions. *Lancet Glob. Health* **2019**, *7*, e1332-e1345. Erratum in: *Lancet Glob. Health* **2023**, *11*, e196.
26. Oliveira, A.B.; Bachi, A.L.L.; Ribeiro, R.T.; Mello, M.T.; Tufik, S.; Peres, M.F.P. Unbalanced plasma TNF- α and IL-12/IL-10 profile in women with migraine is associated with psychological and physiological outcomes. *J. Neuroimmunol.* **2017**, *313*, 138-144.
27. Gold, E.B.; Xing, G.; Avis, N.E.; Harlow, S.; Joffe, H.; Matthews, K.; Pavlovic, J.M.; Thurston, R.C.; Waetjen, E. The longitudinal relation of inflammation to incidence of vasomotor symptoms. *Menopause* **2022**, *29*, 894-904.
28. Serdar, C.C.; Cihan, M.; Yücel, D.; Serdar, M.A. Sample size, power and effect size revisited: simplified and practical approaches in pre-clinical, clinical and laboratory studies. *Biochem. Med. (Zagreb)*. **2021**, *31*, 010502.

29. Harakeh, S.; Kalamegam, G.; Pushparaj, P.N.; Al-Hejin, A.; Alfadul, S.M.; Al Amri, T.; Barnawi, S.; Al Sadoun, H.; Mirza, A.A.; Azhar, E. Chemokines and their association with body mass index among healthy Saudis. *Saudi J. Biol. Sci.* **2020**, *27*, 6-11.
30. Shah, N.R.; Braverman, E.R. Measuring adiposity in patients: the utility of body mass index (BMI), percent body fat, and leptin. *PLoS One* **2012**, *7*, e33308.
31. Whelton, P.K.; Carey, R.M.; Aronow, W.S.; Casey DE, Jr.; Collins, K.J.; Dennison Himmelfarb, C.; DePalma, S.M.; Gidding, S.; Jamerson, K.A.; Jones, D.W.; et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J. Am. Coll. Cardiol.* **2018**, *71*, e127-e248. Erratum in: *J. Am. Coll. Cardiol.* **2018**, *71*, 2275-2279.
32. Zahir, H.; Javaid, A.; Rehman, R.; Hussain, Z. Statistical concepts in biology and health sciences. *J. Ayub Med. Coll. Abbottabad* **2014**, *26*, 95-97.
33. Viero, F.T.; Rodrigues, P.; Frare, J.M.; Da Silva, N.A.R.; Ferreira, M.A.; Da Silva, A.M.; Pereira, G.C.; Ferreira, J.; Pillat, M.M.; Bocchi, G.V.; et al. Unpredictable Sound Stress Model Causes Migraine-Like Behaviors in Mice With Sexual Dimorphism. *Front. Pharmacol.* **2022**, *13*, 911105.
34. Jiang, L.; Cui, Y.; Du, H. Tinnitus constancy and self-reported severe headache or migraine symptoms in peri- and postmenopausal women: a statistical modeling and machine learning analysis. *Eur. J. Med. Res.* **2025**, Dec 23. doi: 10.1186/s40001-025-03712-y.
35. Li, S.; Zhang, J. Association Between Magnesium Intake and Migraine Among Pre and Postmenopausal Women: A Cross-Sectional Study. *Int J Womens Health* **2025**, *17*, 2747-2758.
36. GBD 2016 Neurology Collaborators. Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* **2019**, *18*, 459-480.
37. Vetvik, K.G.; MacGregor, E.A. Sex differences in the epidemiology, clinical features, and pathophysiology of migraine. *Lancet Neurol.* **2017**, *16*, 76-87.
38. Allais, G.; Chiarle, G.; Sinigaglia, S.; Airola, G.; Schiapparelli, P.; Benedetto C. Gender-related differences in migraine. *Neurol. Sci.* **2020**, *41*, 429-436.
39. Ornello, R.; Caponnetto, V.; Frattale, I.; Sacco, S. Patterns of Migraine in Postmenopausal Women: A Systematic Review. *Neuropsychiatr. Dis. Treat.* **2021**, *17*, 859-871.
40. Cutler, J.A.; Sorlie, P.D.; Wolz, M.; Thom, T.; Fields, L.E.; Roccella, E.J. Trends in hypertension prevalence, awareness, treatment, and control rates in United States adults between 1988-1994 and 1999-2004. *Hypertension* **2008**, *52*, 818-827.
41. Bramlage, P.; Pittrow, D.; Wittchen, H.U.; Kirch, W.; Boehler, S.; Lehnert, H.; Hoefler, M.; Unger, T.; Sharma, A.M. Hypertension in overweight and obese primary care patients is highly prevalent and poorly controlled. *Am. J. Hypertens.* **2004**, *17*, 904-910.
42. Shihab, H.M.; Meoni, L.A.; Chu, A.Y.; Wang, N.Y.; Ford, D.E.; Liang, K.Y.; Gallo, J.J.; Klag, M.J. Body mass index and risk of incident hypertension over the life course: the Johns Hopkins Precursors Study. *Circulation* **2012**, *126*, 2983-2989.
43. Linhart, C.; Tukana, I.; Lin, S.; Taylor, R.; Morrell, S.; Vatucaawaqa, P.; Magliano, D.; Zimmet, P. Continued increases in hypertension over three decades in Fiji, and the influence of obesity. *J. Hypertens.* **2016**, *34*, 402-409.
44. Wilson, P.W.; D'Agostino, R.B.; Sullivan, L.; Parise, H.; Kannel, W.B. Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. *Arch. Intern. Med.* **2002**, *162*, 1867-1872.
45. Ho, A.K.; Bartels, C.M.; Thorpe, C.; Pandhi, N.; Smith, M.; Johnson, H.M. Achieving Weight Loss and Hypertension Control Among Obese Adults: A US Multidisciplinary Group Practice Observational Study. *Am. J. Hypertens.* **2016**, *29*, 984-991.
46. Pepine, C.J.; Kerensky, R.; Lambert, C.; Smith, K.; von Mering, G.O.; Sopko, G.; Bairey Merz, C.N. Some thoughts on the vasculopathy of women with ischemic heart disease. *J. Am. Coll. Cardiol.* **2006**, *47*, S30-S35.
47. Scher, A.I.; Terwindt, G.M.; Picavet, H.S.; Verschuren, W.; Ferrari, M.D.; Launer, L.J. Cardiovascular risk factors and migraine: the GEM population-based study. *Neurology* **2005**, *64*, 614-620.

48. Hagen, K.; Stovner, L.J.; Vatten, L.; Holmen, J.; Zwart, J.A.; Bovim, G. Blood pressure and risk of headache: a prospective study of 22 685 adults in Norway. *J. Neurol. Neurosurg Psychiatry*. **2002**, *72*, 463-466.
49. Wiehe, M.; Fuchs, S.C.; Moreira, L.B.; Moraes, R.S.; Fuchs, F.D. Migraine is more frequent in individuals with optimal and normal blood pressure: a population-based study. *J. Hypertens*. **2002**, *20*, 1303-1306.
50. Tzourio, C.; Gagnière, B.; El Amrani, M.; Alpérovitch, A.; Bousser, M.G. Relationship between migraine, blood pressure and carotid thickness. A population-based study in the elderly. *Cephalalgia* **2003**, *23*, 914-920.
51. Gudmundsson, L.S.; Thorgeirsson, G.; Sigfusson, N.; Sigvaldason, H.; Johannsson, M. Migraine patients have lower systolic but higher diastolic blood pressure compared with controls in a population-based study of 21,537 subjects. The Reykjavik Study. *Cephalalgia* **2006**, *26*, 436-444.
52. Melby, M.K.; Murashima, M.; Watanabe, S. Phytochemical intake and relationship to past health history in Japanese women. *Biofactors* **2004**, *22*, 265-9.
53. Jaacks, L.M.; Vandevijvere, S.; Pan, A.; McGowan, C.; Wallace, C.; Imamura, F.; Mozaffarian, D.; Swinburn, B.; Ezzati, M. The obesity transition: stages of the global epidemic. *Lancet Diabetes Endocrinol*. **2019**, *7*, 231-240.
54. Albanese, M.; Ceci, V.; Carrera, G.; Selntigia, A.; Exacoustos, C.; Tiberi, M.; Saracini, S.; Matteocci, A.; Mercuri, N.B.; Chiurchiù, V. Inflammatory Cytokine Signatures Are Associated With Disease Burden and Comorbidity of Episodic Migraine and Endometriosis. *Neurol. Neuroimmunol. Neuroinflamm*. **2025**, *12*, e200490.
55. Vuralli, D.; Ceren Akgor, M.; Gok Dagidir, H.; Gulbahar, O.; Yalinay, M.; Bolay, H. Lipopolysaccharide, VE-cadherin, HMGB1, and HIF-1 α levels are elevated in the systemic circulation in chronic migraine patients with medication overuse headache: evidence of leaky gut and inflammation. *J. Headache Pain* **2024**, *25*, 23.
56. Peterlin, B.L.; Bigal, M.E.; Tepper, S.J.; Urakaze, M.; Sheftell, F.D.; Rapoport, A.M. Migraine and adiponectin: is there a connection? *Cephalalgia* **2007**, *27*, 435-446.
57. Marics, B.; Peitl, B.; Varga, A.; Pázmándi, K.; Bácsi, A.; Németh, J.; Szilvássy, Z.; Jancsó, G.; Dux, M. Diet-induced obesity alters dural CGRP release and potentiates TRPA1-mediated trigeminovascular responses. *Cephalalgia* **2017**, *37*, 581-591.
58. Guldiken, B.; Guldiken, S.; Demir, M.; Turgut, N.; Tugrul, A. Low leptin levels in migraine: a case control study. *Headache* **2008**, *48*, 1103-1107.
59. Cho, S. M.; Park, D.W.; Lee, Y.G.; Jeong, Y.J.; Jeon, H.; Seo, Y.J.; Kim, H.; Kang, S.C. Anti-varicella zoster virus and related anti-inflammation effects of ethanolic extract of *Elaeocarpus sylvestris*. *J. Ethnopharmacol*. **2022**, *287*, 114951.
60. Tirani, S.A.; Saneai, P.; Khorvash, F.; Askari, G. Effects of probiotic and vitamin D co-supplementation on migraine index, quality of life, and oxidative stress in adults with migraine headache: a randomized triple-blinded clinical trial. *Eur. J. Nutr*. **2025**, *64*, 179.
61. Patel, U.K.; Shah, D.; Malik, P.; Hussain, M.; Chauhan, B.; Patel, D.; Sharma, S.; Khan, N.; Patel, K.; Kapoor, A.; Kavi, T. A Comprehensive Assessment of Vascular and Nonvascular Risk Factors Associated with Migraine. *Cureus* **2019**, *11*, e6189.
62. Petelina, T.I.; Avdeeva, K.S.; Bykova, S.G.; Musikhina, N.A.; Gapon, L.I.; Gorbatenko, E.A.; Zueva, E.V.; Leonovich, S.V.; Lystsova, N.L. Nonspecific parameters of the immune inflammatory response as a link in the pathogenesis of remodeling of the vascular wall and destruction of bone tissue in women with arterial hypertension in postmenopausal women. *Klin. Lab. Diagn*. **2019**, *64*, 417-423.
63. Shan, X.; Zhao, X.; Li, S.; Song, P.; Man, Q.; Liu, Z.; Hu, Y.; Yang, L. Association of Serum 25(OH)D with Metabolic Syndrome in Chinese Women of Childbearing Age. *Nutrients* **2022**, *14*, 2301.
64. Azmi, A.; Rismani, M.; Pourmontaseri, H.; Mirzaii, E.; Niknia, S.; Miladpour, B. The role of vitamin D receptor and IL-6 in COVID-19. *Mol. Genet. Genomic Med*. **2023**, *11*, e2172.
65. Motamed, S.; Anari, R.; Motamed, S.; Amani, R. Vitamin D and biomarkers of inflammation and oxidative stress among pregnant women: a systematic review of observational studies. *BMC Immunol*. **2023**, *24*, 41.

66. Arzani, M.; Jahromi, S.R.; Ghorbani, Z.; Vahabizad, F.; Martelletti, P.; Ghaemi, A.; Sacco, S.; Togha, M.; School of Advanced Studies of the European Headache Federation (EHF-SAS). Gut-brain Axis and migraine headache: a comprehensive review. *J. Headache Pain* **2020**, *21*, 15.
67. Ghorbani, Z.; Togha, M.; Rafiee, P.; Ahmadi, Z. S.; Rasekh Magham, R.; Djalali, M.; Shahemi, S.; Martami, F.; Zareei, M.; Razeghi Jahromi, S.; et al. Vitamin D3 might improve headache characteristics and protect against inflammation in migraine: a randomized clinical trial. *Neurol. Sci.* **2020**, *41*:1183-1192.

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