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# Vascular risk assessment in female migraineurs

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## ABSTRACT

**BACKGROUND AND OBJECTIVES:** Migraine is the most common disabling neurological disorder, twice as common in females as compared to males. It has been associated with increased vascular risk leading to cardiovascular disease and stroke. The underlying pathophysiology remains unclear, as the results are inconsistent. This study was designed to see if migraine alone, excluding traditional risk factors, is a predictable cause of untoward vascular events.

**METHODOLOGY:** A cross-sectional comparative study was conducted on female migraineurs with a history of varying migraine duration, compared to controls. Participants were divided into three groups of 28 subjects each. Serum homocysteine, highly sensitive C-Reactive Protein and total cholesterol were measured. Data was analyzed with SPSS version 17.0.

**RESULTS:** Median with interquartile range was calculated. Comparison of the groups with Kruskal-Wallis ANOVA revealed a non-significant difference among the three groups. The estimated p-value for Hcy, hsCRP and total cholesterol was 0.479, 0.819 and 0.978, respectively. Levels of Hcy, hsCRP, and total cholesterol were also explored as categories: normal, moderately elevated, and highly elevated. A non-significant difference was observed among the groups.

**CONCLUSION:** The vascular risk profile of migraineurs does not differ from that of healthy females, even if the migraine is present for a longer duration.

**KEYWORDS:** Migraine, Risk Assessment, Cardiovascular Disease, Homocysteine, High Sensitive C-reactive Protein.

## INTRODUCTION

Migraine is a primary headache disorder. It is the second most common disabling disease with a prevalence of 14% [1]. Although present in all ages and both sexes, women are twice as likely to suffer from migraine, even though the prevalence falls after midlife. According to the Global Burden of Disease Study report 2024, ischemic heart disease and stroke have been the leading causes of mortality since 1991 across the globe [2]. Over the years, studies have linked migraine to increased risk of untoward vascular events [3].

Subjects suffering from migraine have been suggested to be at increased risk of cerebral, coronary, retinal, peripheral and dermal vascular involvement. Proposed mechanisms for headache are implicated to involve cerebral blood vessels along with the changes that are taking place in blood vessels, which might be pro-coagulatory, atherosclerotic or related to vasomotion [4,5]. The endothelium maintains homeostasis, which can be disrupted by smoking, elevated LDL cholesterol, diabetes mellitus, hypertension and acute or chronic inflammatory conditions. All are considered traditional risk factors for CVD [6].

Homocysteine (Hcy) is a cysteine-containing amino acid, generated from the metabolism of methionine in sulphur containing amino acids. Excessive oxidation of Hcy results in the formation of free radicals, which may lead to cell damage. Homocysteine in plasma is of the oxidised form, and 70-80% is bound to albumin. The remaining 20-30% exists as the reduced form and mixed disulfides as homocysteine-cysteine and combinations. Free Hcy or reduced Hcy comprises approximately 1% of total Hcy [7].

Serum homocysteine (Hcy) levels vary with age and gender, with slightly higher levels in men than in women. Levels tend to increase with advancing age, likely due to declining renal function and depletion of vitamin B12 stores. The normal reference range for serum homocysteine is 5–15 µmol/L. Age-specific values indicate an average level of approximately 10.8 µmol/L in individuals aged 40–42 years, rising to around 12.48 µmol/L in those aged 65–67 years.

Hyperhomocysteinemia is classified as moderate (15–30 µmol/L), intermediate (31–100 µmol/L), and severe (>100 µmol/L) [8]. Even a modest increase of 10–15% in homocysteine levels is associated with a 10% increase in the risk of coronary artery disease.

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Elevated homocysteine contributes to endothelial dysfunction by inducing oxidative stress, which promotes inflammatory processes and accelerates atherosclerosis [6]. Furthermore, meta-analytic evidence demonstrates a positive correlation between elevated homocysteine levels and the incidence of myocardial infarction and stroke [9].

C-reactive protein is a circulating pentraxin composed of five 23-kilodalton (kDa) subunits. It is an alpha globulin, assembled as a cyclic pentamer. It is an acute-phase reactant synthesized in the liver in the presence of inflammation in the body. It has a pleiotropic effect in the body. Normal values for adult serum range from 0.068 to 8.2 mg/L. Levels above 10 mg/dL mark the presence of acute inflammation. The greater the inflammation, the higher the levels.

In the absence of acute inflammation, the levels should be less than 10 mg/L measured by a highly sensitive method. High hsCRP levels predict the risk of cardiovascular events [10]. Cholesterol is present in the body in free and esterified forms. Intracellular storage of cholesterol is present in esterified forms. High cholesterol levels may lead to increased uptake by vascular macrophages, which can turn them into foam cells. This leads to the accumulation of LDL and initiation of localised vascular inflammation. Atherosclerosis is the pathological process that occurs due to the the accumulation of cholesterol in the intimal layer of the vascular endothelium. One of the important functions of vascular endothelium is the maintenance of cholesterol homeostasis [11]. The normal value for serum total cholesterol is less than 200 mg/dL. Values above 200 up to 239 mg/dl are considered borderline. Values above 240 mg/dL are considered high.

Migraine has been added as a risk factor for cardiovascular disease and stroke by QRISK3 in 2017. Adding migraine with aura to traditional risk scoring improves risk estimation in the Reynolds Risk score model and AHA/ACC guidelines [12]. These tools are developed after large prospective cohorts. However, migraine alone has not been studied as an independent risk factor, excluding the traditional risk factors. The present study aimed to enrol comparatively young migraineurs with varying durations without traditional risk factors. Inflammatory markers (hsCRP, total cholesterol) are established biomarkers for risk assessment of cardiovascular disease, whereas a marker for endothelial dysfunction (Hcy) was selected as associated with increased risk of stroke [13].

## METHODOLOGY

A comparative cross-sectional study was conducted at the Physiology Department, Postgraduate Medical Institute, Lahore, from November 2014 to August 2015. Approval from the ethical committee of Postgraduate Medical Institute and Advanced Studies & Research Board, UHS was obtained (ref no. UHS/Education/126-10/3074). Sample size was calculated using PASS 2008 software (Power Analysis and Sample Size Software). With 90% power of the study and a level of significance of 5%. The total sample was calculated to be N = 84 subjects, and the number of subjects in each of the three groups was n = 28. Migraineurs between the ages of 20 and 50 years were selected from the Outpatient Department, Lahore General Hospital, Lahore. Employees of the hospital were also invited to participate. Sampling was done by non-probability purposive sampling. Healthy subjects were mostly selected from relatives of migraineurs and from PGMI employees.

Inclusion criteria for controls: healthy females 20 to 50 years of age. Inclusion criteria for migraineurs: females aged between 20 and 50 years, diagnosed as migraineurs by the health care professionals or by interviewing the subjects in detail.

Exclusion criteria for controls were pregnancy, known cases of diabetes, hypertension, and ischemic heart disease, primary headaches, presence of acute or chronic inflammatory disease, use of steroids, acute or chronic rhinitis, use of non-steroidal anti-inflammatory agents in the past one week (however, they were included after keeping them medicine-free for one week) and menopause. Exclusion criteria for migraineurs included history of migraine for less than six months, pregnancy, known cases of diabetes, hypertension, ischemic heart disease, headaches other than migraine, presence of chronic inflammatory disease, use of steroids, acute or chronic rhinitis, use of non-steroidal anti-inflammatory agents in the past one week however they were included after keeping them medicine free for one week and menopause.

Subjects were divided into three study groups. Group A comprised of migraineurs with a history of migraine for less than ten years. Group B had migraineurs with a history of migraine for more than ten years. Group C had normal healthy females with no history of migraine or any other type of headache.

Subjects fulfilling the inclusion criteria were included in the study. A detailed history was taken to confirm migraine and exclude other types of headaches. Written informed consent was taken from the subjects.

Blood Samples were taken after 12 hours of fasting. After completing aseptic measures, 5 ml of venous blood was drawn in a sitting position [14]. Blood was immediately transferred to a gel vacutainer. Blood samples were stored on ice packs until they were carried to the laboratory. Samples were centrifuged at 2500 rev/min for 10 minutes. Serum was obtained and saved [15].

Serum homocysteine was measured according to the manufacturer's instructions using the Axis Homocysteine Enzyme Immunoassay Kit (Axis Shield Diagnostics Limited, Dundee, United Kingdom).

C-reactive protein was determined by a high-sensitivity enzyme immunoassay test kit of Biocheck, Inc., Foster City, CA. The determination of CRP was performed with an automated analyzer. The hsCRP estimation was based on the principle of a solid-phase sandwich enzyme-linked immunosorbent assay.

Serum total cholesterol was estimated using the CHOD-PAP method with a kit from Fortress Diagnostics, Antrim, UK, on a spectrophotometer (Hitachi, Japan). Cholesterol concentration in the sample is measured by

using the following formula:

Cholesterol Concentration in sample = ▲absorbance sample / ▲absorbance standard × Concentration of standard

Data entry and analysis were conducted using the Statistical Package for the Social Sciences (SPSS) version 17.0. Data normality was tested using the Shapiro-Wilk test. Quantitative variables were presented as median with interquartile range. The Kruskal-Wallis ANOVA test was applied to determine statistical significance. Medians of groups were compared pairwise using the Mann-Whitney U test. Categorical variables were compared using the Chi-square test and Fisher's Exact Test, and p-values were determined. Statistical significance was set at $p < 0.05$.

## RESULTS

84 women, aged 20-50 years, were divided into three groups of 28 subjects each. The Mean ± SD age of subjects in group A was 28.6 ± 8.8 years, Group B 39.50 ±7.70 years and Group C 33.63±8.57 years. A comparison of median serum homocysteine (µmol/L), C-reactive protein (mg/L) and serum total cholesterol (mg/dL) is summarised in Table-I for the three groups. Mean rank for each group was determined for all three variables (Table-II). A Kruskal-Wallis ANOVA was applied, and no significant difference was observed. The estimated p-value for Hcy was 0.479, p-value for hsCRP=0.819, p-value for total cholesterol = 0.978 (Table-II).

Serum Hcy, CRP and cholesterol levels were also explored by categories summarized in Table-III. Serum Hcy level was categorised as normal if < 15 µmol/L, moderately elevated if between 15-30 µmol/L and high if above 30 µmol/L. The value of CRP was considered normal if it was less than 3.0 mg/L, the level was considered high between 3.0 and 7.0 mg/L and very high if it was more than 7.0 mg/L. Cholesterol levels below 200 mg/dL were considered normal. Values between 200-240 mg/dl were considered moderately elevated, whereas serum total cholesterol levels more than 240mg/dl were considered high.

Cholesterol levels less than 200 mg/dL were stated normal. Values between 200-240 mg/dl were considered moderately elevated whereas serum total cholesterol levels more than 240mg/dl were considered high.

**Table-I: Comparison of Serum Homocysteine, hsCRP and total Cholesterol levels in the study groups.**

| Group | Hcy | CRP (mg/L) | Cholesterol (mg/dL) |
|---|---|---|---|
| | Median (IQR) | Median (IQR) | Median (IQR) |
| Group A | 13.0 (16.7-7.3) | 3.41 (4.55-2.05) | 180 (199-146) |
| Group B | 9.7 (15-3,5) | 3.26 (6.17-2.18) | 171 (202-149) |
| Group C | 7.3 (15.9-2) | 3.73 (9.09-2.02) | 164 (199-150) |

**Table-II: Comparison of serum homocysteine, CRP and total cholesterol among the study groups.**

| Group | Hcy | CRP | Cholesterol |
|---|---|---|---|
| | Mean Rank | | |
| Group A | 46.64 | 40.23 | 42.70 |
| Group B | 41.98 | 43.02 | 43.07 |
| Group C | 38.88 | 44.25 | 41.73 |
| **Chi-square value** | 1.47 | 0.40 | 0.05 |
| **P-value** | 0.479 | 0.819 | 0.978 |

***P-value calculated using kruskal wallis ANOVA.**

**Table-III: Comparison of Serum Hcy, CRP, total Cholesterol by categories among three study groups.**

| Group | Homocysteine (µmol/L) | | | CRP (mg/L) | | | Cholesterol (mg/dL) | | | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| | < 15.0 | 15.0 - 29.9 | ≥30.0 | < 3.0 | 3.0 - 7.0 | >7.0 | < 200 | 200 - 240 | > 240 | |
| | n(%) | n(%) | n(%) | n(%) | n(%) | n(%) | n(%) | n(%) | n(%) | n(%) |
| Group A | 16(57.1) | 10(35.7) | 2(7.1) | 12(42.9) | 12(42.9) | 4(14.3) | 21(75.0) | 7(25.0) | 0(0.0) | 28(100) |
| Group B | 19(67.9) | 9(32.1) | 0(0.0) | 12(42.9) | 11(39.3) | 5(17.9) | 20(71.4) | 7(25.0) | 1(3.6) | 28(100) |
| Group C | 18(64.3) | 9(32.1) | 1(3.6) | 12(42.9) | 7(25.0) | 9(32.1) | 22(78.6) | 4(14.3) | 2(7.1) | 28(100) |
| **Total** | 53(63.1) | 28(33.3) | 3(3.6) | 36(42.9) | 30(35.7) | 18(21.4) | 63(75.0) | 18(21.4) | 3(3.6) | 84(100) |
| **P-Value** | 0.779 ** | | | 0.447* | | | 0.599 ** | | | |

***P-value calculated using chi-square test ** P-value calculated using Fisher exact test.**

## DISCUSSION

The present study aimed to exclude traditional risk factors and determine whether migraine alone is a risk factor for adverse vascular events. Subjects of the study were women aged between 20 and 50 years. All were non-smokers, normotensive, non-diabetic, without any illness causing acute or chronic inflammation. None were using steroids and/or any nonsteroidal anti-inflammatory agents at the time of study.

In our study, homocysteine levels did not meet the criteria for hyperhomocysteinemia; however, the median homocysteine level was 13 µmol/L among subjects with migraine and a disease duration of less than 10 years. The median level in the control group (no migraine) was 7.3 µmol/L. The difference is 5.7 µmol/L. For every 2.5 µmol/L difference in total Hcy level, the risk of cardiovascular event increases by 10% and for stroke by 20%[16]. The differences in serum Hcy, hsCRP, and total cholesterol were not statistically significant among the three groups, even if the migraine had been present for a longer period of time. In a comprehensive review of biomarkers linked to migraine, it is shown that higher Hcy levels are present in migraine with aura only[17].

Yilmaz Avci (2019) found the same results as ours in a case-control study, of which Hcylevels were not different between cases and controls. However, the CRP levels were higher in migraineurs. The difference might be due to the fact that sampling in this study was done during migraine attacks [18]. A nutritional survey also suggests that Hcy and CRP levels are elevated before a headache attack. Administration of vitamin B1, B6, and B12 supplements improves the intensity, duration, and frequency of migraine headaches [19]. In a prospective population-based cohort, the risk was estimated using the Systemic Coronary Risk Evaluation (SCORE2) and its association with prevalent and incident migraine. In the present study, White Europeans were at the highest risk, whereas Asians represented the lowest-risk group. Individuals at risk of adverse vascular events were those who had traditional risk factors. The majority of female migraineurs belonged to the lowest-risk category (SCORE2 <1.0). These findings in women were consistent across age groups, both below and above 50 years [20].

This study suggests a healthier cardiovascular profile in migraine patients, consistent with our findings. Elevated levels of hsCRP have been reported in chronic migraine, indicating a possible association with increased risk; however, none of our patients met the criteria for chronic migraine[21]. Van Welie (2023) reviewed the lipid profiles of migraineurs and found inconsistent results across studies, likely due to methodological differences. Although migraineurs did not exhibit generalised dyslipidemia, women demonstrated more deranged lipid profiles compared to men, which may reduce their protective advantage[22]. In our study, no significant difference in total cholesterol levels was observed between groups.

Our study is strong because each patient was included after a thorough diagnostic interview. No cases were self-reported. We excluded subjects with traditional risk factors based on history and physical exam.

**LIMITATIONS:**

Due to limited resources, all factors proposed to link migraine to CVD and stroke could not be explored. The history of medicine intake was taken, but couldn't be produced due to a lack of sufficient evidence. The parameters need to be studied after classifying migraine into the subgroups.

## CONCLUSION

Serum Hcy, hsCRP and total cholesterol are established risk factors for an untoward vascular event. No difference was seen in these parameters in the migraineurs compared to healthy women (even if the migraine is present for a long duration, i.e., more than ten years).

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**Authors Contributions:**

**Aysha Zaheer:** Conception, design of the work, data acquisition and drafting the work.

**Shama Iqbal:** Data acquisition.

**Sauda Usmani:** Data interpretation and critically reviewing the manuscript.

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