Original Article

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# Vascular Risk Factors and Biomarkers of Endothelial Dysfunction in Chronic Migraine Patients- A Cross-sectional Study

Internal Medicine Section

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## ABSTRACT

**Introduction:** The available literature on vascular risk and endothelial dysfunction in patients with Chronic Migraine (CM) is limited. CM patients are known to have a higher risk of cardiovascular and cerebrovascular events. The present study aims to characterise the vascular risk and endothelial dysfunctions in CM patients and compare them with Healthy Controls (HC).

**Aim:** To assess the vascular risk factors and biomarkers of endothelial dysfunction in CM patients and compare them with healthy non-headache controls.

**Materials and Methods:** This cross-sectional study was conducted from October 2021 to January 2023 at the headache clinic of GB Pant Institute of Postgraduate Medical Education and Research in Delhi, India. The patients were diagnosed with CM using the International Classification of Headache Disorders-3 (ICHD-3) criteria. The patients were drug-naïve for preventive medications and did not have medication overuse headache. Clinical vascular risk factors such as Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Ankle Brachial Index (ABI), Body Mass Index (BMI), and Waist Hip Ratio (WHR) were measured. A battery of biochemical vascular risk factors, including serum C-reactive protein, leptin, insulin, fasting and post-prandial glucose, Glycosylated Haemoglobin (HbA1c), lipid profile, lipoprotein-A, pro-Brain Natriuretic Peptide (pro-BNP), and serum biomarkers of endothelial dysfunction like Intercellular Adhesion Molecules-1 (ICAM-1), Myeloperoxidase (MPO), Interleukin-6 (IL-6), Tumour Necrosis Factor-Alpha (TNF-alpha), Asymmetric Dimethyl Arginine (ADMA), fibrinogen, and von Willebrand's factor were measured in all patients during the interictal period. Statistical analysis was done using the Statistical Package for Social Sciences (SPSS) version 25.0, and the Mann-Whitney U test, student's t-test, and Chi-square tests were applied.

**Results:** Thirty-two patients with CM and thirty-two non-headache healthy subjects were included in the study (age 30.6±8.8 years; 29 females and 3 males) vs. (31.7±7.9 years; 19 females and 13 males, respectively). Compared to HC, CM patients had significantly higher DBP (81.0±8.0 mmHg vs. 66.2±6.2 mmHg; p<0.001). Among the biochemical parameters, CM patients had higher post-prandial blood sugar (mg/dL) (140.2±10.7 vs. 136.6±7.0; p=0.021), HbA1c (%) (5.8±0.8 vs. 5.6±0.4; p=0.034), serum cholesterol (mg/dL) (146.9±36.2 vs. 131±20.8), and Triglyceride (TG) levels (mg/dL) (93.2±10.8 vs. 88.5±13.0; p=0.001) compared to HCs. Among the biomarkers of endothelial dysfunction studied, levels of ICAM-1 (pg/mL) (4.5±3.8 vs. 1.3±0.62; p<0.001), MPO (pg/mL) (415.4±266.0 vs. 108.9±141.4; p=0.001), IL-6 (pg/mL) (10.8±4.9 vs. 4.2±1.5; p<0.001), and ADMA (ng/mL) (32.6±28.3 vs. 23.5±22.1; p=0.008) were higher in the CM group compared to non-headache controls.

**Conclusion:** This study found that patients with CM have significantly higher vascular risk and evidence of endothelial dysfunction compared to healthy non-headache controls. The significantly elevated biomarkers of endothelial dysfunction may possibly be related to persistent neurogenic inflammation in CM and require further exploration through larger studies.

**Keywords:** International classification of headache disorders-3, Inflammation, Intercellular adhesion molecule-1

## INTRODUCTION

Migraine is a common disabling disorder characterised by recurrent episodes of headache attacks. It is the third most prevalent medical condition and the second most disabling neurological disorder in the world [1]. Based on the frequency of headache attacks, the International Classification of Headache Disorders-3 (ICHD-3) recognises two types of migraine, namely Episodic Migraine (EM) and CM [2]. CM is defined as a headache occurring on ≥15 days/month for more than three months, having features of migraine headache on at least eight days/month. CM is a highly disabling condition and is often associated with acute medication overuse. Risk factors for conversion from episodic to CM include female gender, obesity, acute migraine medication overuse, inappropriate and ineffective use of acute treatment, depression, and stressful life events [3]. CM sufferers are more likely to be older, have a higher BMI, have lower educational levels, have lower household income, and are less likely to be employed than EM sufferers [4].

Various studies in the last two decades have shown that migraine patients also have an increased vascular risk profile, namely obesity, hypertension, dyslipidemia, metabolic syndrome, and various markers of increased atherosclerosis compared to the general population [5,6]. A large meta-analysis of a population cohort showed that female migraineurs and those with aura have an increased risk of myocardial infarction and stroke [6].

It is postulated that CM patients, who share a higher proportion of vascular risk factors than EM, may be more predisposed to vascular risk [4,7]. However, the mechanisms underlying the association between migraine and cardiovascular and cerebrovascular disorders remain unknown. Possible mechanisms that have been postulated include enhanced atherosclerosis, unknown genetic factors, inflammatory arteriopathy due to recurrent neuroinflammation, and endothelial dysfunction. However, only a handful of studies have comprehensively assessed the clinical and biochemical risk factors of increased atherosclerosis and the serum biomarkers of endothelial dysfunction in CM patients.

Therefore, this study aimed to evaluate the clinical and biochemical vascular risk factors and the serum biomarkers of endothelial dysfunction using a battery of tests in patients with CM and compare them with healthy non-headache controls.

## MATERIALS AND METHODS

This was a cross-sectional study conducted from October 2021 to January 2023. The subjects were consecutive migraine patients attending the Headache Clinic at GB Pant Institute of Postgraduate Medical Education and Research (GIPMER) in Delhi. The study was approved by the Institutional Ethics Committee (IEC: GIPMER/(83/01/2021/342), and informed written consent was obtained from all participants.

### Chronic Migraine (CM) Patients

**Inclusion criteria:** Patients aged 18 to 50 years who fulfilled the diagnostic criteria for CM as laid down by ICHD-3 [2], and those who were drug-naive for preventive treatments were included in this study as cases.

**Exclusion criteria:** Patients with other secondary headaches, including medication overuse headache, as well as pregnant or lactating individuals, those on chronic anti-inflammatory or immunomodulatory drugs, statins, antihypertensives, nitrates, or anti-epileptic drugs, and females using oral contraceptives were excluded from the study.

### Healthy Non-headache Controls

**Inclusion criteria**: Healthy individuals without headaches were included from hospital staff, friends of the patients, and attendants of admitted neurology patients (subjects with a history of episodic tension-type headache were allowed, but they did not have an episode of headache in the last three months).

**Exclusion criteria:** Subjects with acute or chronic painful conditions and/or those using anti-inflammatory agents on a regular basis, as well as pregnant or lactating individuals, and those using oral contraceptives were excluded from the controls of the study.

**Sample size calculation:** Sample size was calculated based on estimates from previous studies on vascular risk associations, specifically IL-6 levels (435.28±19.04 pg/mL vs. 259.00±32.92 pg/mL), CRP levels (718.11±42.71 mg/dL vs. 514.21±47.04 mg/dL), and TNF-alpha levels (651.04±26.99 pg/mL vs. 448.95±43.89 pg/mL) for chronic migraineurs and controls, respectively [7]. Assuming 80% power and a 5% alpha error, with a 1:1 ratio of two groups, the sample size was estimated to be 32 patients in each group.

### Procedure

**Assessment:** All patients were evaluated using a detailed structured proforma that covered all aspects of the clinical characteristics of headache. This included the duration of disease onset, attack duration, attack frequency, location, character, pre-monitory symptoms, systemic symptoms such as nausea, vomiting, photophobia, and phonophobia, as well as clinical autonomic symptoms/signs, triggers, motor and psychological symptoms during headache, and postdrome. Detailed family history for headache was also obtained. Relevant biochemical tests (haemogram, liver function tests, kidney function tests, thyroid function tests) and radiological tests were performed to exclude secondary causes. The severity of pain was rated using the Visual Analogue Scale (VAS). The impact of headache was assessed using the Headache Impact Test (HIT-6), and headache-related disability was assessed using the Migraine Disability Assessment Test (MIDAS). A baseline screening headache diary for one month was utilised before inclusion in the study.

**Clinical vascular risk factors:** A battery of clinical vascular risk factors, such as SBP, DBP, ABI, BMI, and WHR, were measured. The auscultatory method of Blood Pressure (BP) measurement with a properly calibrated and validated sphygmomanometer was used. Subjects were instructed to sit comfortably in a chair for at least five minutes with their arm supported at heart level. The appropriate cuff size (bladder length 80% and width at least 40% of arm circumference) was used to ensure accuracy. The systolic BP was defined as the appearance of the first sound (Korotkoff phase 1), and the diastolic BP was defined as the disappearance of the sound (Korotkoff phase 5). Additionally, resting brachial and ankle blood pressures were measured in the supine position on both extremities, five minutes apart, and the mean pressure was recorded to calculate the ABI. For BMI, height was measured in centimeters using a wall-mounted stadiometer, and weight (kg) was determined using a weighing scale with a minimum measuring unit of 100 gm. BMI was calculated as the weight in kilograms divided by the square of height in meters. Waist Circumference (WC) was measured midway between the inferior margin of the last rib and the crest of the ileum, and Hip Circumference (HC) was measured around the pelvis at the point of maximum protrusion of the buttocks, both in a horizontal plane without compressing the soft tissues. WC and HC were recorded to the nearest cm, and WHR was defined as the ratio of WC to HC.

**Biochemical vascular risk factors:** Venous blood (10 mL) was collected under aseptic conditions by experienced laboratory technicians from the participants after an eight-hour fast. It was allowed to clot at 25°C for 30 minutes, followed by centrifugation at 8000 rpm for 20 minutes. Subsequently, the serum was separated, and aliquots were prepared. The following biochemical vascular risk factors were measured: high-sensitivity C-reactive Protein (hsCRP) using a fully automatic autoanalyser c501 Hitachi/Roche (Germany), fasting serum leptin using Enzyme Linked Immunosorbent Assay (ELISA) from Mannheim, Germany, fasting adiponectin using ELISA, fasting serum insulin using electrochemiluminescence with commercially available kits e411 provided by Elecsys, Roche Diagnostics, fasting and post-prandial glucose (2 hours after 75 gm of glucose), HbA1c, lipid profile including serum cholesterol, Low-Density Lipoprotein (LDL), Triglycerides (TG), and High-Density Lipoprotein (HDL), Lipoprotein (a) [LP(a)], and proB-type Natriuretic Peptide (BNP).

**Biomarkers of endothelial dysfunction:** Venous blood (10 mL) was collected under aseptic conditions by experienced laboratory technicians from the participants after an eight-hour fast. It was allowed to clot at 25°C for 30 minutes, followed by centrifugation at 8000 rpm for 20 minutes. Subsequently, the serum was separated, and aliquots were prepared. A battery of biomarkers of endothelial function was measured, including serum levels of ICAM-1, MPO, IL-6, TNF-alpha, ADMA, fibrinogen (measured using Elitepro Instrumentation Laboratory), and von Willebrand's factor (all measured using commercially available ELISA kits).

## STATISTICAL ANALYSIS

Statistical analysis was performed using the SPSS software package (version 25). Categorical data were summarised as frequencies and percentages. Continuous data were summarised as means, and Student's t-test was used to compare the means. Non-parametric analyses, such as the Mann-Whitney U test, were used for parameters that were not normally distributed. Post-hoc Bonferroni adjustments were made for multiple testing. The Chi-square test with Yates correction and Fisher's-exact test were used to compare proportions between the groups. The level of significance was set at $p<0.05$.

## RESULTS

Sixty-four subjects, including thirty-two patients with CM and thirty-two non-headache healthy subjects, were studied. The mean age of the patients with CM was 30.6±8.8 years, compared to 31.7±7.9 years in the non-headache group (p=0.594). There were 29 females (91%) in the CM group, compared to 19 females (59.4%) in the non-headache group (p=0.004). The age and sex distribution is shown in [Table/Fig-1].

| Demographic data of subjects | Case group Chronic Migraine (CM) (n=32) | Non-headache healthy controls (HC) (n=32) |
|---|---|---|
| **Age** | | |
| Age (years) (mean±SD) | 30.6±8.8 | 31.7±7.9 |
| Age range (years) | 18-50 | 19-50 |
| Median (years) | 33.5 | 33 |
| **Sex (n)** | | |
| Male (M) | 3 | 13 |
| Female (F) | 29 | 19 |

**[Table/Fig-1]:** Demographic Distribution of all study subjects.

The headache burden of the CM patients is presented in [Table/Fig-2]. On average, the CM patients experienced 23.4±4.7 headache days per month, of which 17.9±4.6 were migraine days. They also had significant headache impact and disability, as indicated by their mean HIT-6 and MIDAS scores.

| Headache characteristics | Chronic migraine (CM) (n=32) |
|---|---|
| Duration of illness (years) | 6.7±4.5 |
| Attack duration if untreated (hours) | 9.9±3.4 |
| Attack duration if treated with acute medication (hours) | 2.4±1.3 |
| Migraine days per month | 17.9±4.6 |
| Headache days per month | 23.4±4.7 |
| Headache attack severity (by Visual Analog Scale) | 6.5±0.6 |
| HIT-6 Score | 66.7±3.8 |
| MIDAS Score | 30.1±13.8 |

**[Table/Fig-2]:** Headache burden of Chronic Migraine (CM) patients.
*All values shown are mean±SD

Compared to the non-headache group, CM patients had significantly higher DBP (81.0±8.0 vs. 66.2±6.2; p<0.001). They also had higher BMI, but the differences did not reach statistical significance (27.2±2.3 vs. 24.9±1.8; p=0.099). These results are shown in [Table/Fig-3].

| Clinical parameters | Chronic Migraine (CM) | Non-headache controls | p-value |
|---|---|---|---|
| SBP (mmHg) | 117.4±12.7 | 119.4±11.6 | 0.629 |
| DBP (mmHg) | 81.0±8.0 | 66.2±6.2 | **<0.001** |
| Ankle Brachial Index (ABI) | 0.98±0.01 | 0.99±0.01 | 0.071 |
| Body Mass Index (BMI) (kg/m$^2$) | 27.2±2.3 | 24.9±1.8 | 0.099 |
| Waist Hip Ratio (WHR) | 0.91±0.03 | 0.93±0.036 | 0.162 |

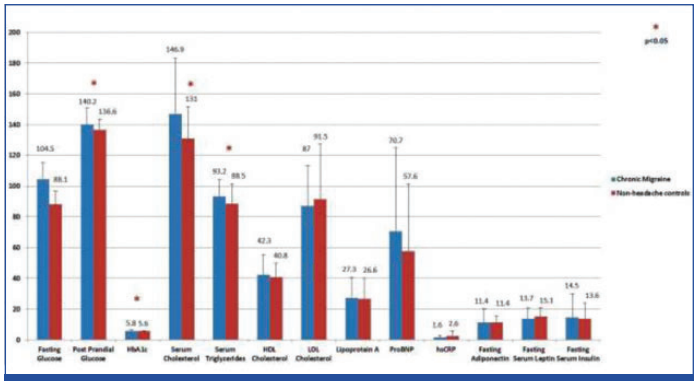
**[Table/Fig-3]:** Comparison of clinical vascular risk factors in patients of Chronic Migraine (CM) vs. non-headache controls.
*All values shown are mean±SD

Among the biochemical parameters, CM patients had higher post-prandial blood sugar (mg/dL) (140.2±10.7 vs. 136.6±7.0; p=0.021), HbA1c (%) (5.8±0.8 vs. 5.6±0.4; p=0.034), serum cholesterol (mg/dL) (146.9±36.2 vs. 131±20.8), and TG levels (mg/dL) (93.2±10.8 vs. 88.5±13.0; p=0.001) compared to the non-headache group. The comparison of the biochemical vascular risk factors between the two groups is shown in [Table/Fig-4].

Among the biomarkers of endothelial dysfunction that were studied, levels of ICAM-1 (pg/mL) (4.5±3.8 vs. 1.3±0.62; p<0.001), MPO (pg/mL) (415.4±266.0 vs. 108.9±141.4; p=0.001), IL-6 (pg/mL) (10.8±4.9 vs. 4.2±1.5; p<0.001), and ADMA (ng/mL) (32.6±28.3 vs. 23.5±22.1; p=0.008) were higher in the CM group compared to the non-headache controls [Table/Fig-5].

## DISCUSSION

It was found that patients with CM had significantly higher vascular risk, along with evidence of endothelial dysfunction, compared to non-headache healthy controls. Patients with CM had higher DBP, post-prandial blood sugar, HbA1c, serum cholesterol, and TG




**[Table/Fig-4]:** Comparison of biochemical vascular risk factors between the patients of CM and non-headache controls.

| Endothelial parameters | Chronic Migraine (CM) | Non-headache controls | p-value |
|---|---|---|---|
| ICAM-1 (ng/mL) | 4.5±3.8 | 1.3±0.62 | **<0.001** |
| Myeloperoxidase (MPO) (pg/mL) | 415.4±266.0 | 108.9±141.44 | **0.001** |
| Interleukin-6 (IL-6) (pg/mL) | 10.8±4.9 | 4.2±1.5 | **<0.001** |
| TNF-alpha (pg/mL) | 13.5±5.9 | 11.6±6.1 | 0.213 |
| Asymmetric Dimethyl Arginine (ADMA)(ng/mL) | 32.6±28.3 | 23.5±22.1 | **0.008** |
| Fibrinogen (mg/dL) | 389.8±118.8 | 355.6±131.8 | 0.951 |
| vWF (ng/mL) | 4.4±2.9 | 5.0±3.0 | 0.571 |

**[Table/Fig-5]:** Comparison of markers of endothelial dysfunction in patients of Chronic Migraine (CM) vs. non-headache controls.

levels. These vascular risk factors have been strongly associated with cardiovascular and cerebrovascular diseases [5,8,9].

Previously, Mathew NT reported that patients with chronic daily headache, originally transformed from EM, had a higher likelihood of hypertension [10]. Bigal ME et al., conducted a randomised case-control study to identify factors associated with induction and transformation from episodic to CM [11]. They found a strong association between hypertension and CM, with and without analgesic overuse, when comparing the study group to EM and chronic post-traumatic headache. In contrast, Huang Q et al., found that the frequency of elevated BP was not higher in CM patients compared to the non-CM group [12]. They suggested that analgesic overuse maybe the reason for the higher frequency of elevated BP in patients with chronic daily headaches and its subtypes. However, patients with CM and analgesic overuse were excluded from their study. Interestingly, several population-based studies, such as those by Shechter A et al., Gudmundsson LS et al., and the HUNT study by Winsvold BS et al., have also found that DBP is higher in migraine patients compared to non-migraine controls [13-15]. Furthermore, in a recent study by Ramusino MC et al., hypertension was proposed to have contributed to the chronic evolution of headache through mechanisms shared with migraine, such as vascular tone alteration and autonomic dysregulation [16]. It is important to note that although DBP was higher among migraineurs, it still fell within the normal range according to JNC8 guidelines [17]. Hence, clinically overt hypertension may be related to disease duration and the extent of vascular risk that accumulates over time. Supporting this argument, some longitudinal population-based studies have found that migraine patients are more likely to develop clinical hypertension, particularly diastolic hypertension, over time [18,19].

Among the studied biochemical vascular risk factors, previous studies have demonstrated altered glucose metabolism and abnormal lipid profile levels in migraineurs compared to controls. Thus, the present results are consistent with these previous studies [20-24]. A recent review article by Islam MR and Nyholt DR found that the comorbidity of migraine and glucose-related traits

may have complex pathogenic mechanisms, including impaired glucose homeostasis, insulin resistance, reduced cerebrovascular reactivity, abnormal brain metabolism, shared genetic factors, neurotransmitters, and sex hormones [25]. Furthermore, several studies have found a bidirectional link between migraine and insulin resistance and type 2 diabetes.

Similarly, a meta-analysis of observational studies on serum lipid abnormalities in migraine was conducted by Liampas I et al., which included 17 studies (16 case-control and 1 cross-sectional) [26]. The results were compatible with higher LDL-C levels in migraine patients compared to healthy controls (12 studies, Mean Difference (MD)=10.4 mg/dL, 95% Confidence Interval (CI)=(1.6, 19.2)). Similarly, higher total cholesterol levels were found in migraine patients (14 studies, MD=10.6 mg/dL, 95% CI=(1.8, 19.3)), as well as higher TG levels (15 studies, MD=11.8 mg/dL, 95% CI=(3.6, 20.0)). However, HDL-C concentrations did not differ between the two groups. Subgroup analyses and comparisons between migraine with aura and migraine without aura individuals showed no significant differences. However, direct comparisons between CM patients and controls were not presented.

The mechanism underlying the association between migraine and cardiovascular and cerebrovascular disorders is currently unknown. Various mechanisms, including endothelial dysfunction, have been postulated to account for the increased risk of vascular diseases in migraine patients [26,27]. Broadly speaking, endothelial dysfunction primarily results in impaired endothelial-dependent vasodilation, due to a decrease in the bioavailability of vasodilating factors and an increase in endothelium-derived vasoconstrictors [28]. Additionally, endothelial activation, characterised by a proinflammatory and procoagulatory environment, enhances atherogenesis and vascular diseases. Endothelial dysfunction can be assessed through serum biomarkers and vascular reactivity studies. However, recent studies on biomarkers of endothelial dysfunction in migraine patients have yielded conflicting results [29,30].

In the present study, among the biomarkers of endothelial dysfunction, ICAM-1, MPO, IL-6, and ADMA levels were significantly elevated in CM patients compared to non-headache controls. ICAM-1 is a cell surface glycoprotein expressed on endothelial, immune, and epithelial cells and belongs to the Ig superfamily [31]. It plays a role in leukocyte transendothelial migration and in innate and adaptive responses to inflammation. MPO is found in the aniline blue granules of myeloid cells (neutrophils and monocytes) [32]. It plays a role in phagocytosis and microorganism killing. Reactive oxygen species derived from MPO promote the development of tissue damage and disease. MPO is also involved in atherosclerosis and cardiovascular and cerebrovascular diseases. IL-6 is released by macrophages, B and T-cells, eosinophils, and basophils and plays a role in the induction and control of acute phase protein synthesis, stimulation of haematopoiesis, stimulation of antibody production by B-cells, neutrophil activation, macrophage maturation, and increased expression of IL-1 and TNF-α [33]. ADMA is formed through the proteolysis of methylated residues of arginine and causes endothelial dysfunction due to low levels of NO [34]. High plasma ADMA levels have a strong positive correlation with cardiovascular and cerebrovascular events. These biomarkers of endothelial dysfunction have been found to be elevated in migraine patients in general, but not many studies have specifically explored the differences between CM and HCs. A recent study by Togha M et al., showed that serum levels of IL-6, CRP, and TNF-α were significantly higher in subjects with CM compared to EM and controls [7].

The present study found significantly elevated levels of multiple biomarkers of endothelial dysfunction (4 out of 7 measures) in CM patients using a battery of tests. This raises the possibility of their role in the increased vascular risk factors observed in CM patients [35]. The endothelium modulates vascular function and structure primarily through the production of nitric oxide, which protects the vasculature against the development of atherosclerosis and thrombosis. Endothelial dysfunction is associated with hypertension, contributing to inflammation in the vascular wall of resistance arteries, as well as increased lipoprotein oxidation, smooth muscle cell proliferation, extracellular matrix deposition, cell adhesion, and thrombus formation in conducting arteries [35]. Similarly, abnormalities in glucose metabolism and lipid abnormalities have been linked to endothelial dysfunction [36,37].

It is noteworthy that the absolute values of various parameters that were estimated were mostly within normal cut-offs. Therefore, while the comparisons between the two groups showed statistical significance, the clinical significance of these findings remains uncertain.

### Limitation(s)

The present study cohort had a shorter duration of CM, which may have influenced the results. Additionally, there was a significantly higher proportion of females in the CM group compared to the controls. However, it is known that CM has a significantly higher female preponderance [38].

Furthermore, the exact pathophysiology of CM remains uncertain, although atypical pain processing, central sensitisation, cortical hyperexcitability, and neurogenic inflammation have been implicated in its development [38]. In this context, the findings of the present study, which showed significantly elevated biomarkers of endothelial dysfunction possibly related to persistent neurogenic inflammation in CM, are important and warrant further exploration through larger studies.

## CONCLUSION(S)

The results of this study suggest a higher occurrence of biomarkers in CM patients compared to non-headache HCs. Therefore, when treating a CM patient, it is important to assess vascular risk factors through a thorough history, clinical examination, and relevant biochemical investigations.

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