ORIGINAL ARTICLE

LINK BETWEEN PREMATURE CARDIOVASCULAR DISEASE AND HYPERHOMOCYSTEINEMIA

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Background: Hyperhomocysteinemia, characterized by elevated homocysteine levels, is recognized as a significant risk factor for premature cardiovascular disease (CVD) due to its role in endothelial dysfunction and atherogenesis. This study aims to measure the homocysteine concentration in CVD patients and determine the link between homocysteine levels and premature CVD. **Methods:** This prospective cohort study was conducted on 350 subjects after their consent and randomly selected after approval by the IRB. The sample size was calculated using OpenEpi. In the experimental group, 200 patients with unstable angina, non-ST, and ST-elevation myocardial infarction were included. After 10 hours of fasting, blood samples were taken and homocysteine concentrations were measured with an ELISA kit (Rochester). Wilcoxon test was applied and $p \leq 0.05$ was considered significant. **Results:** Most of the subjects fell in older age groups. Family history of CVD was present in 41% of patients, 48% had non-ST and ST-elevation MI, 7% were post-myocardial infarction, and 3% patients had recurrent myocardial infarction. There was an increased concentration of homocysteine in the experimental groups compared to controls (25±0.1 µmol/L *vs* 5.71±0.2 µmol/L). The differences were more significant in ST-elevation than in other conditions and the control group. **Conclusion:** Homocysteine levels were elevated in CVD with the highest concentration observed in ST-elevation MI. It is important to monitor homocysteine levels in patients with a family history of cardiovascular disease or a history of myocardial infarction. Elevated homocysteine levels may be useful biomarker for assessing cardiovascular risk.

Keywords: Homocysteine, Hyperhomocysteinemia, Premature cardiovascular disease, Early diagnosis

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INTRODUCTION

Cardiovascular Disease (CVD) accounts for extensive morbidity and mortality in all countries and age groups. There are severe presentations of the disease at markedly early onset, which further burden the healthcare systems. Clinical determinants of cardiovascular disease including hypertension, diabetes, dyslipidaemia, and tobacco smoking have been well-established but recent studies indicate that patients with early onset cardiovascular disease frequently exhibit elevated levels of homocysteine, a novel non-conventional risk factor. Homocysteine is a sulfur amino acid that is formed during the metabolism of methionine and has aroused much interest in recent years as being an independent risk factor for atherosclerosis.[1]

Hyperhomocysteinemia is defined as the excess of homocysteine levels and has been shown to promote atherosclerosis, endothelial injury, and thromboembolic activity leading to premature cardiovascular disease. The essential causal relationship linking cardiovascular disease with hyperhomocysteinemia is its vasculotoxic effects, encouraging oxidative stress and increased clotting, all of which lead to a higher risk of myocardial infarction (MI), stroke, and other cardiovascular diseases.[2]

Even though some studies have pointed out the possible correlation between high levels of homocysteine and risk for cardiovascular events, the exact importance of this amino acid in premature cardiovascular disease with special emphasis on different types of myocardial infarctions is still saved for future research works.[3]

Homocysteine has been established as an independent risk factor for CVD.[4] Hyperhomocysteinemia has been associated with myocardial infarction and unstable angina.[5–6] There is a need for further research focusing on the reduction of homocysteine levels as a potential strategy for the prevention of premature cardiovascular events.[7]

This study aims to measure the homocysteine concentration in CVD patients and determine the link between homocysteine levels and premature CVD.

METHODOLOGY

This prospective cohort study was conducted in Central Park Medical College and Teaching Hospital Lahore from 14th December 2023 to 20th March 2024 on 350 subjects after random collection and was approved by

the Institutional Review Board (IRB# CPMC/IRB-No/1443) of Central Park Medical College and Teaching Hospital. The sample size was calculated using OpenEpi. Informed consent was obtained from all participants before inclusion in the study. This study was conducted in patients diagnosed with unstable angina, and ST and non-ST elevation myocardial infarction. Patients having blood disorders, acute and chronic chest infections, pregnancy, autoimmune disease cardiomyopathy, valvular heart disease, and congenital heart diseases were excluded.

After 10 hours of fasting blood samples were taken between 8 to 10 AM in the next morning. Plasma was immediately separated by centrifugation for 15 minutes at 1,000 rpm at 4 °C. Plasma was stored at -70 °C. Homocysteine concentrations were measured using an ELISA kit (Rochester) according to the guidelines of the kit manufacturer. Wilcoxon test was applied to the data analyzed using SPSS-23.

RESULTS

Participants were categorized into 4 age brackets: 30–40 years (40, 11.42%), 41–50 years (55, 15.7%), 51–60 years (170, 48.6%), and 61–65 years (85, 24.28%). This distribution shows a concentration of participants in the older age groups, a majority of the population in the study fell within the 51–60 year age group, relevant for studying conditions like premature CVD. (Table-1).

Table-1: Age distribution of the participants

Age Groups	Number	Percentage
30–40 Years	40	11.42
41–50 Years	55	15.7
51–60 Years	170	48.6
61–65 Years	85	24.28

The average homocysteine levels were 25±0.1 µmol/L in the experimental groups and 5.71±0.2 µmol/L in the control group. (Table-2).

Table-2: Homocysteine levels in Control and Experimental Groups

Group	Homocysteine Levels (µmol/L)
Experimental Group	25±0.1 µmol/L
Control Group	5.71±0.2 µmol/L

Family history of CVD was present in 41% of patients, 48% had non-ST and ST-elevation MI, 7% were post-myocardial infarction, and 3% patients had recurrent myocardial infarction. (Figure-1).

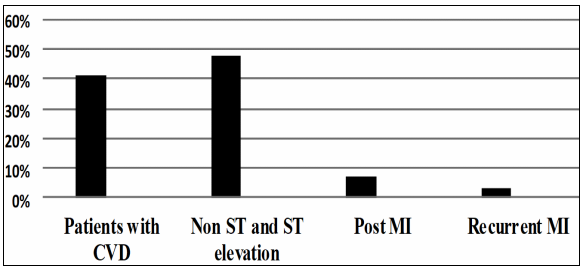

Figure-1: Associated conditions in patients

Higher circulating levels of homocysteine were associated with an increased risk of ST elevation, non-ST elevation MI, and unstable angina. For ST elevation the odds ratios were 1.11 (95% CI: 1.03–1.21, p=0.01) for non-ST-elevation myocardial infarction (NSTEMI), 1.26 (95% CI: 1.05–1.5, p=0.01) for ST-elevation myocardial infarction (STEMI), and 1.11 (95% CI: 1.03–1.21, p=0.07) for unstable angina.

Table-3: Association of homocysteine level with CVD

Condition	Odds Ratio	95% CI	*p*
STEMI	1.26	1.05–1.5	0.01
NSTEMI	1.11	1.03–1.21	0.01
Unstable Angina	1.11	1.03–1.21	0.07

DISCUSSION

Increased levels of homocysteine have been proposed as a potential marker for premature cardiovascular disease. Several studies have suggested a positive correlation between elevated homocysteine levels and the risk of CVD. Homocysteine, an amino acid derived from methionine metabolism, is implicated in the pathogenesis of atherosclerosis, thrombosis, and endothelial dysfunction, all of which are key components of cardiovascular disease.[8]

Some research suggests that homocysteine may not act as an independent risk factor for CVD, meaning its impact on cardiovascular health isn't solely explained by its association with other risk factors such as hypertension, hyperlipidemia, or smoking. This suggests that even in individuals without traditional risk factors, elevated homocysteine levels may still contribute to CVD risk.[9] Homocysteine is considered an important and independent risk factor for the development of cardiovascular diseases. Atherosclerosis develops with time due to calcification of intima, lipid deposition, increased permeability of vessels, and injury to the intimal layer. It develops due to increased concentration of C-reactive protein, oxidative damage, and increased collagen synthesis in arterial walls. Homocysteine causes increased synthesis of collage in arterial walls and causes the development of cardiovascular disease.[10]

As its proposed role as a marker for premature CVD, monitoring homocysteine levels could potentially aid in the early detection of cardiovascular risk, allowing for preventive interventions to be implemented before the onset of overt symptoms or complications.[11,12]

Hyperhomocysteinemia can be caused by the deficiency of vitamin B complex and it causes injury to vascular smooth muscles. McCully[2] studied the increased concentration of homocysteine found in patients of cancer, alcoholics, smokers, diabetic, and hyperuricemic patients as well. Hyperhomocysteinemia can also depend on age, genetics, and dietary patterns.[13] Fuchs *et al*[13] demonstrated that vegetarians tend to have

higher concentrations of homocysteine compared to non-vegetarians, likely due to a deficiency in vitamin B_{12}, which is primarily found in animal products such as meat. Yuan *et al*[14] in a study conducted on 80 female patients for 14 years reported that there was a lower incidence of CVD in the group who was treated with vitamins as a substitutive therapy, which decreased homocysteine levels, as compared to those who were not treated with therapy.

Hyperhomocysteinemia is recognized as a risk factor for CVD. Development of atherosclerosis is complex, influenced by additional factors such as genetics, lifestyle habits, and excess weight. These factors do not act in isolation in the progression of cardiovascular diseases. To strengthen the evidence and enhance our understanding, larger-scale studies involving diverse populations are recommended to make broader observations.

CONCLUSION

Homocysteine levels were elevated in all three conditions of CVD with the highest concentration observed in ST-elevation MI. These findings highlight the importance of monitoring homocysteine levels, especially in patients with a family history of cardiovascular disease or a history of myocardial infarction. Elevated homocysteine levels may serve as a useful biomarker for assessing cardiovascular risk.

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