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To Evaluate the Significance of Hyperhomocysteinemia in Patients with Coronary Artery Disease

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Abstract: ***Coronary artery disease (CAD) is considered to be the most common cause of mortality worldwide from the last some years (from 1990s). Homocysteine is described as the promoter for atherosclerotic disorder in the middle aged. Here in this study we are going to evaluate the relationship between levels of serum homocysteine with coronary artery disease. It has been shown that fasting serum homocysteine levels in CAD patients were higher than the patients without coronary artery disease. Whereas the rise of Homocysteine levels in a patient with coronary artery disease, increases the severity of CAD. This is the reason behind the implication of homocysteine as a novel risk factor for Coronary artery disease in the entire world. Though many studies in this regard failed to demonstrate the direct correlation between CAD and homocysteine levels. In the general prospective population of aged men, it is considered that high homocysteine level is common and strongly associated with coronary heart disease and coronary artery disease yet its contribution in young patients is uncertain. Although some studies have revealed that vitamin B12 is the major cause of increased homocysteine but vitamin supplementation can be used to decrease the level of homocysteine and prevent the patient from CAD risk. As a whole and according to all the data, it suggests that homocysteine is not a cause of CAD but it can be considered as a marker which leads to the risk of it. Therefore to prevent the threat all the necessary precautions need to be taken by the patient and a proper medical check up is also mandatory. Following the medical guidelines any patient can get rid of from the risk of CAD by proper diet and by decreasing the homocysteine level.***

Keywords: Hyperhomocysteinemia, coronary artery disease (CAD), Homocysteine, Endothelial dysfunction, folic acid, human serum

1. Introduction

Homocysteine is an amino acid which was first discovered in 1932 and got enlisted in the biochemical background. As it shows almost the same chemical properties like cystine, hence it got familiar with the name Homocysteine. Homocysteine (Hcy) is basically a sulfhydryl amino acid which involves itself in the metabolism of methionine and derived from it. Heating of sulphuric acid to the amino acid methionine resulted in the production of homocysteine. In the year of 1955 for the first time Vincent du Vigneaud was awarded with Nobel Prize for this innovative discovery of biochemically important sulphur compounds and particularly for the very first synthesis of Polypeptide hormone. (Nobel Media AB, 2013) In animal Homocysteine considered as an abundant protein. (Venes, 2017)

The explanation of hyperhomocysteinemia differs in regards to different studies. (Faeh, 2006) Presence of homocysteine in the blood in an abnormally high level (above 15 µmol/L) designated as hyperhomocysteinemia in medical study. (Guo, 2009) In a healthy human being (fasting) the total concentration of homocysteine in plasma is low and its average level is in between 5.0 and 15.0 µmol/L when estimated with the help of HPLC or between 5.0-12.0 µmol/l when examined by immunoassay methods. (Baszczuk, 2014) According to different populations, different age groups, diet and genetic background the pervasiveness of hyperhomocysteinemia may vary. Homocysteine levels may increase in blood due to smoking, consumption of coffee, male sex, high blood pressure, faulty diet etc. (Shenoy, 2014) On the other hand, homocysteine levels may sustain in lower concentration by maintaining physical activity, moderate alcohol consumption, good folate and vitamin B12. (Shenoy, 2014)

Coronary artery disease (CAD) is considered as the most common type of heart disease which is the main leading cause of death in both men and women in the United States. Not only the US but it has also become the major health problem worldwide. It has been scientifically proven that in the world the main reason behind mortality and morbidity is CAD. (Zylberstein, 2004) Arteries are known as the supplier of the blood to the heart so any fundamental changes in the arteries can cause major heart issues. The coagulation of cholesterol and other material, namely plaque, starts building up in the inner walls of arteries and making it narrowed and hardened which results in the improper blood circulation to the heart muscle and cause heart related diseases. The build up is known as Atherosclerosis. As it grows simultaneously, the walls of the arteries become narrower and for which less blood can pass through it, so the heart is unable to get the proper amount of blood or oxygen it requires. This circumstances leads to a massive chest pain (angina) or may cause heart attack. (Schaffer, 2014) Not only heart attack but also in heart failure and arrhythmias CAD is considered to be the main reason. CAD weakens the heart muscle which manipulates the normal beating rhythm of the heart and which causes Arrhythmias and sometimes it disturbs the normal pumping system of the heart for that rest of the body is unable to receive the proper amount of blood it requires for functioning.

The relation between hyperhomocysteinemia and coronary artery disease (CAD) has been significantly described in several studies. (Nygård et al., 1995; Clarke et al., 1991) Hyperhomocysteinenia considers to be as the risk factor for CAD which encouraged the study related to

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homocysteine and recognition of factors modulate its activities. (Robinson, 1995) For the first time in 1996 Bethesda Conference recognized that left ventricular hypertrophy, hyperhomocysteinemia, lipoprotein (a) excess, hypertriglyceridemia, hyperfibrinogenemia (among other thrombogenic factors), and oxidative stress as potential risk factors for CAD in any adult individual. The serum concentration of homocysteine acknowledged being one of the main reasons of stroke and heart related diseases. (Boushey et al., 1995) Still there was doubt regarding the association in between CAD and homocysteine. (Eikelboom, 1999) Nygard et al. have demonstrated a basic relation between Hcy and overall mortality rate of a person by the help of Angiography (imaging test by the help of X-rays to view patient's body's blood vessels) and came to the conclusion that the increasing amount of Homocysteine can be responsible for demonstrating CAD. (Rasmussen et al., 1996)

Several methods are there to diagnose CAD which involves electrocardiogram, echocardiogram, CT scan etc. but among those angiograms is considered to be the best method to indicate the reason behind the disease. After the diagnosis the doctor prescribes medicine to the patient accordingly based upon their age, physical strength, and other health issues. In a bigger picture it has been declared that CAD has increased through the last three decades in low and middle income countries including India and it has been found that 20% of the deaths in India are because of CAD. Presently CAD is considered as the leading cause of death worldwide. An estimated study has been revealed that 3.8 billion men and 3.4 million women die each year from this disease. (Mackay, 2004)

Various studies have revealed that the reason behind the association between Hcy and CAD may vary according to age group, environment, physical strength, habits etc. To get the proper justification and to come to the conclusion, this study has been carried out to signify the impact of hyperhomocysteinemia in patients with coronary artery disease.

2. Aim and Objectives

Aim

- This study aimed to analyze the association of hyperhomocysteinemia or homocysteine with the patient of coronary heart disease.
- To study the role of homocysteine levels as a risk factor compared to other risk factors for the development of CAD

Objectives

- To characterize the importance of Homocysteine Levels.
- To evaluate the significance of hyperhomocysteinemia in patients with coronary artery disease.

3. Materials and Methods

This descriptive observational study was done in Mahatma Gandhi Mission Medical College Aurangabad. Total numbers of patients included were 62. The study was done from April 2019 to March 2020. Patients were diagnosed to have Coronay Artery Disease on the basis of Coronary angiography report. The patients were evaluated thoroughly. Detailed history was taken and clinical examination was done. Routine laboratory investigations were done and serum homocysteine levels were evaluated and levels more than 15 umol/l were taken as patient having hyperhomocystenemia. The data was analysed and the results are as follows.

4. Results

Descriptive Statistics

Table 1: Summary of Age/Gender

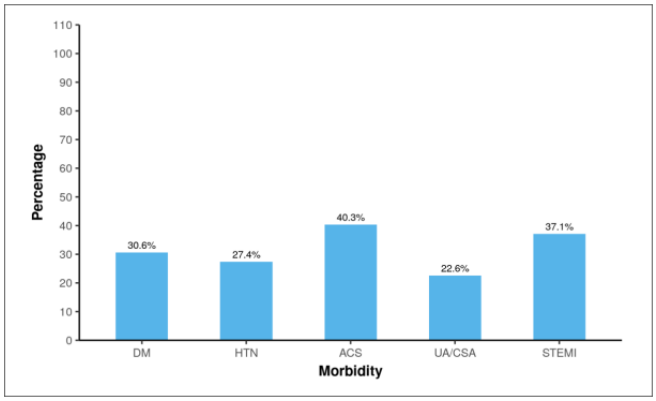
Age/Gender	Mean ± SD||Median (IQR)||Min-Max||Frequency (%)
Age (Years)	52.53 ± 11.04 || 50.00 (45.00-60.00) || 32.00 - 77.00
Age Group	
≤40 Years	10 (16.1%)
>40 Years	52 (83.9%)
Gender	
Male	42 (67.7%)
Female	20 (32.3%)

The mean Age (Years) was 52.53 ± 11.04.

10 (16.1%) of the participants had Age Group: ≤40 Years. 52 (83.9%) of the participants had Age Group: >40 Years. 42 (67.7%) of the participants had Gender: Male. 20 (32.3%) of the participants had Gender: Female.

Table 2: Summary of Morbidity

Morbidity	Present	Absent
DM	19 (30.6%)	43 (69.4%)
HTN	17 (27.4%)	45 (72.6%)
ACS/NSTEMI	25 (40.3%)	37 (59.7%)
UA/CSA	14 (22.6%)	48 (77.4%)
STEMI	23 (37.1%)	39 (62.9%)



19 (30.6%) of the participants had DM: Present. 43 (69.4%) of the participants had DM: Absent.
17 (27.4%) of the participants had HTN: Present. 45 (72.6%) of the participants had HTN: Absent.

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25 (40.3%) of the participants had ACS: Present. 37 (59.7%) of the participants had ACS: Absent.
14 (22.6%) of the participants had UA/CSA: Present. 48 (77.4%) of the participants had UA/CSA: Absent.
23 (37.1%) of the participants had STEMI: Present. 39 (62.9%) of the participants had STEMI: Absent.

Table 3: Distribution of the Participants in Terms of Serum Homocysteine (µMol/L) (n = 62)

Serum Homocysteine (µMol/L)	
Mean (SD)	18.38 (13.88)
Median (IQR)	13.25 (10.37-20.04)
Range	6.56 - 87.8

The variable Serum Homocysteine (µMol/L) was not normally distributed (Shapiro-Wilk Test: p = <0.001).
The mean (SD) of Serum Homocysteine (µMol/L) was 18.38 (13.88). The median (IQR) of Serum Homocysteine (µMol/L) was 13.25 (10.37-20.04). The Serum Homocysteine (µMol/L) ranged from 6.56 - 87.8.

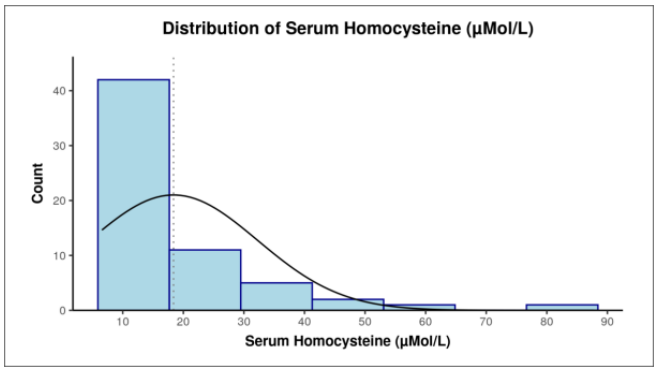
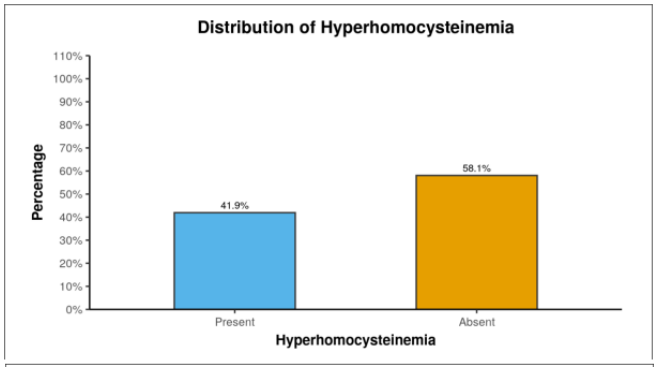
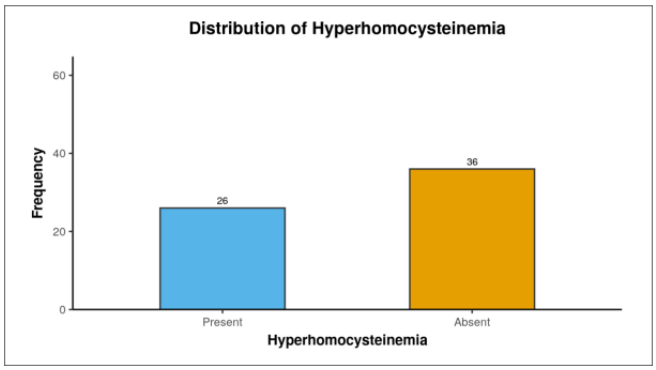


Table 4: Distribution of the Participants in Terms of Hyperhomocysteinemia (n = 62)

Hyperhomocysteinemia	Frequency	Percentage
Present	26	41.9%
Absent	36	58.1%
Total	62	100.0%

41.9% of the participants had Hyperhomocysteinemia: Present. 58.1% of the participants had Hyperhomocysteinemia: Absent.





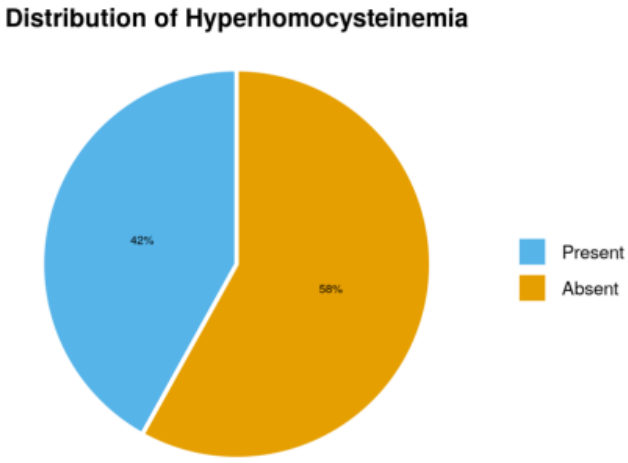


Table 5: Association between Hyperhomocysteinemia and Parameters

Parameters	Hyperhomocysteinemia		p value
	Present (n = 26)	Absent (n = 36)	
Age (Years)	51.12 ± 11.60	53.56 ± 10.66	0.402[1]
Age Group			0.729[2]
≤40 Years	5 (50.0%)	5 (50.0%)	
>40 Years	21 (40.4%)	31 (59.6%)	
Gender			0.189[3]
Male	20 (47.6%)	22 (52.4%)	
Female	6 (30.0%)	14 (70.0%)	
DM (Present)	9 (47.4%)	10 (52.6%)	0.564[3]
HTN (Present)	8 (47.1%)	9 (52.9%)	0.615[3]
ACS/ NSTEMI (Present)	7 (28.0%)	18 (72.0%)	0.068[3]
UA/CSA (Present)	5 (35.7%)	9 (64.3%)	0.592[3]
STEMI (Present)* **	14 (60.9%)	9 (39.1%)	0.020[3]

****Significant at p<0.05, 1: t-test, 2: Fisher's Exact Test, 3: Chi-Squared Test*

The following variables were significantly associated (p<0.05) with the variable 'Hyperhomocysteinemia':, STEMI

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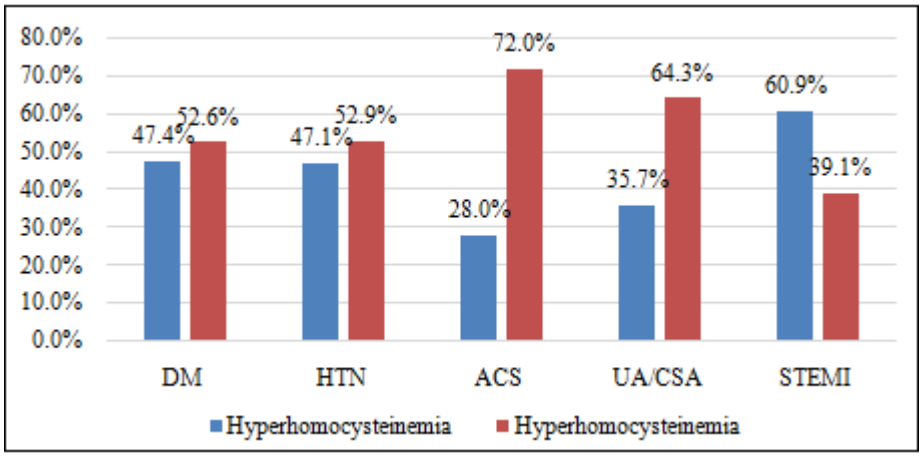


Table 6: Comparison of the 2 Subgroups of the Variable Hyperhomocysteinemia in Terms of Age (Years) (n = 62)

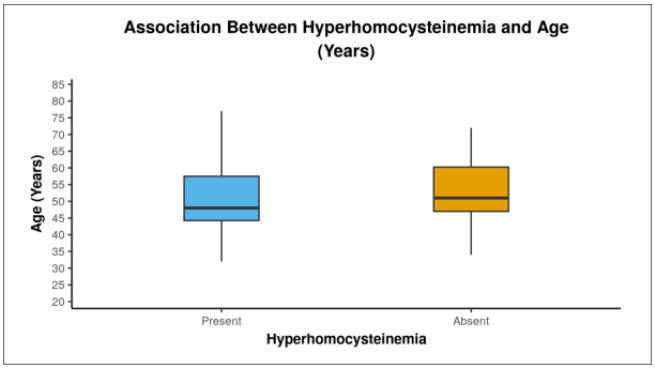
Age (Years)	Hyperhomocysteinemia		t-test	
	Present	Absent	t	p value
Mean (SD)	51.12 (11.60)	53.56 (10.66)	-0.845	0.402
Median (IQR)	48 (44.25-57.5)	51 (47-60.25)		
Range	32 - 77	34 - 72		

The variable Age (Years) was normally distributed in the 2 subgroups of the variable Hyperhomocysteinemia. Thus, parametric tests (t-test) were used to make group comparisons.

The mean (SD) of Age (Years) in the Hyperhomocysteinemia: Present group was 51.12 (11.60). The mean (SD) of Age (Years) in the Hyperhomocysteinemia: Absent group was 53.56 (10.66). The median (IQR) of Age (Years) in the Hyperhomocysteinemia: Present group was 48 (44.25-57.5). The median (IQR) of Age (Years) in the Hyperhomocysteinemia: Absent group was 51 (47-60.25). The Age (Years) in the Hyperhomocysteinemia: Present ranged from 32 - 77. The Age (Years) in the Hyperhomocysteinemia: Absent ranged from 34 - 72.

There was no significant difference between the groups in terms of Age (Years) ($t = -0.845$, $p = 0.402$).

The Box-and-Whisker plot below depicts the distribution of Age (Years) in the 2 groups. The middle horizontal line represents the median Age (Years), the upper and lower bounds of the box represent the 75th and the 25th centile of Age (Years) respectively, and the upper and lower extent of the whiskers represent the Tukey limits for Age (Years) in each of the groups.



The bar graph below depicts the means of Age (Years) in the 2 different groups.

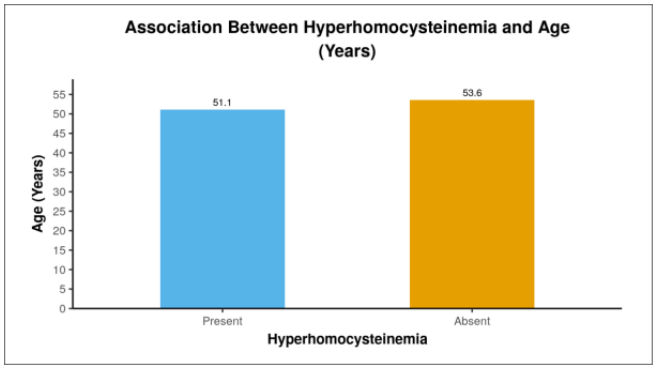


Table 7: Association between Hyperhomocysteinemia and Age Group (n = 62)

Age Group	Hyperhomocysteinemia			Fisher's Exact Test	
	Present	Absent	Total	$\chi 2$	P Value
≤40 Years	5 (50.0%)	5 (50.0%)	10 (100.0%)	0.318	0.729
>40 Years	21 (40.4%)	31 (59.6%)	52 (100.0%)		
Total	26 (41.9%)	36 (58.1%)	62 (100.0%)		

Fisher's exact test was used to explore the association between 'Hyperhomocysteinemia' and 'Age Group' as more than 20% of the total number of cells had an expected count of less than 5.

There was no significant difference between the various groups in terms of distribution of Hyperhomocysteinemia ($\chi 2 = 0.318$, $p = 0.729$).

50.0% of the participants in the group [Age Group: ≤40 Years] had [Hyperhomocysteinemia: Present]. 40.4% of the participants in the group [Age Group: >40 Years] had [Hyperhomocysteinemia: Present]. 50.0% of the participants in the group [Age Group: ≤40 Years] had [Hyperhomocysteinemia: Absent]. 59.6% of the participants in the group [Age Group: >40 Years] had [Hyperhomocysteinemia: Absent].

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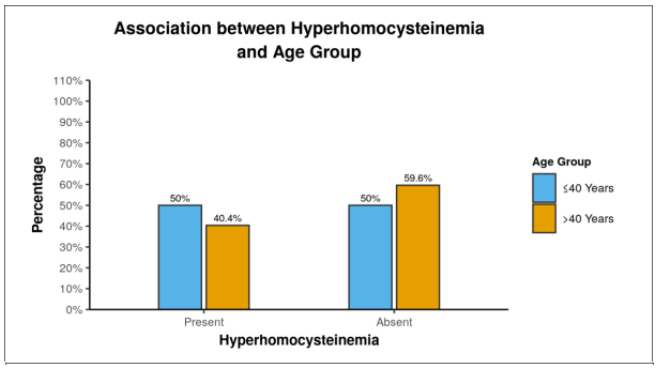


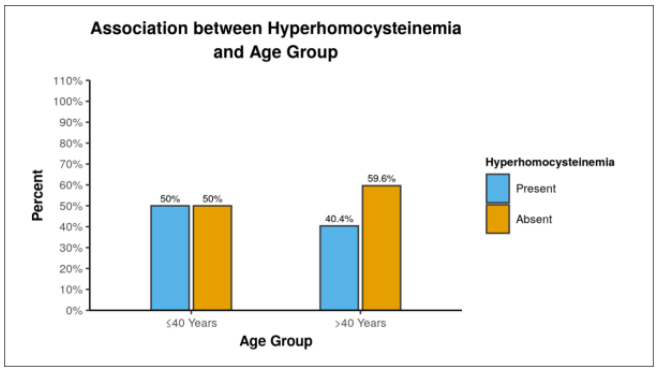


Table 8: Odds Ratios and Relative Risks

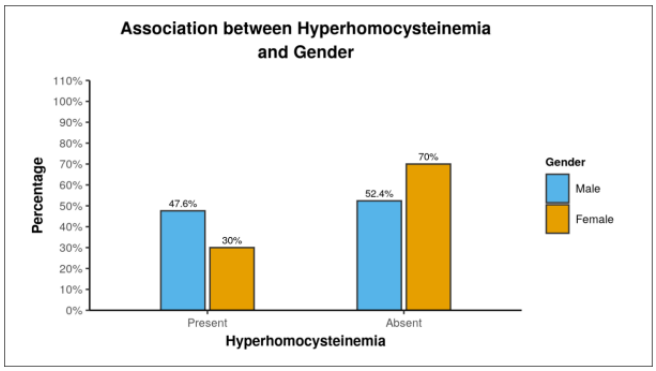
Predictor/Risk Factor	Outcome	Odds Ratio (95% CI)	Relative Risk (95% CI)
Age Group: ≤40 Years	Hyperhomocysteinemia: Present	1.48 (0.38-5.74)	1.24 (0.55-2.23)
Age Group: ≤40 Years	Hyperhomocysteinemia: Absent	0.68 (0.17-2.63)	0.84 (0.39-1.4)
Age Group: >40 Years	Hyperhomocysteinemia: Present	0.68 (0.17-2.63)	0.81 (0.45-1.81)
Age Group: >40 Years	Hyperhomocysteinemia: Absent	1.48 (0.38-5.74)	1.19 (0.71-2.59)
Hyperhomocysteinemia: Present	Age Group: ≤40 Years	1.48 (0.38-5.74)	1.38 (0.47-4.07)
Hyperhomocysteinemia: Present	Age Group: >40 Years	0.68 (0.17-2.63)	0.94 (0.71-1.18)
Hyperhomocysteinemia: Absent	Age Group: ≤40 Years	0.68 (0.17-2.63)	0.72 (0.25-2.15)
Hyperhomocysteinemia: Absent	Age Group: >40 Years	1.48 (0.38-5.74)	1.07 (0.85-1.41)

Table 9: Association between Hyperhomocysteinemia and Gender (n = 62)

Gender	Hyperhomocysteinemia			Chi-Squared Test	
	Present	Absent	Total	$\chi 2$	P Value
Male	20 (47.6%)	22 (52.4%)	42 (100.0%)	1.727	0.189
Female	6 (30.0%)	14 (70.0%)	20 (100.0%)		
Total	26 (41.9%)	36 (58.1%)	62 (100.0%)		

Chi-squared test was used to explore the association between 'Hyperhomocysteinemia' and 'Gender'.

There was no significant difference between the various groups in terms of distribution of Hyperhomocysteinemia ($\chi 2$ = 1.727, p = 0.189). 47.6% of the participants in the group [Gender: Male] had [Hyperhomocysteinemia: Present]. 30.0% of the participants in the group [Gender: Female] had [Hyperhomocysteinemia: Present]. 52.4% of the participants in the group [Gender: Male] had [Hyperhomocysteinemia: Absent]. 70.0% of the participants in the group [Gender: Female] had [Hyperhomocysteinemia: Absent].



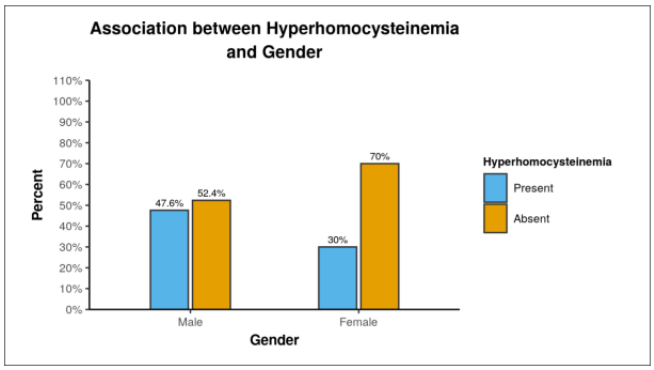


Table 10: Odds Ratios and Relative Risks

Predictor/Risk Factor	Outcome	Odds Ratio (95% CI)	Relative Risk (95% CI)
Gender: Male	Hyperhomocysteinemia: Present	2.12 (0.68-6.58)	1.59 (0.82-3.46)
Gender: Male	Hyperhomocysteinemia: Absent	0.47 (0.15-1.46)	0.75 (0.5-1.17)
Gender: Female	Hyperhomocysteinemia: Present	0.47 (0.15-1.46)	0.63 (0.29-1.22)
Gender: Female	Hyperhomocysteinemia: Absent	2.12 (0.68-6.58)	1.34 (0.85-1.99)
Hyperhomocysteinemia: Present	Gender: Male	2.12 (0.68-6.58)	1.26 (0.88-1.79)
Hyperhomocysteinemia: Present	Gender: Female	0.47 (0.15-1.46)	0.59 (0.26-1.27)
Hyperhomocysteinemia: Absent	Gender: Male	0.47 (0.15-1.46)	0.79 (0.56-1.13)
Hyperhomocysteinemia: Absent	Gender: Female	2.12 (0.68-6.58)	1.69 (0.79-3.84)

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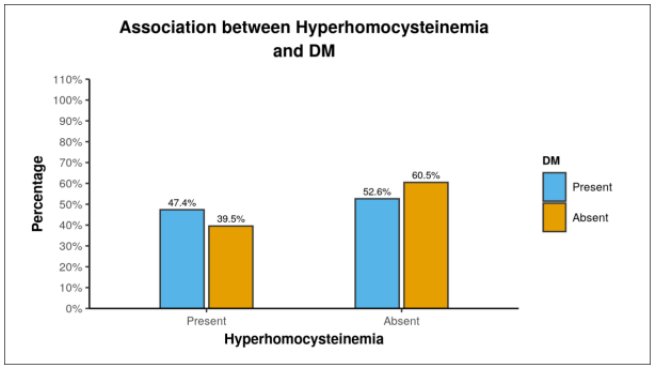
Table 11: Association BetweenHyperhomocysteinemia and DM (n = 62)

DM	Hyperhomocysteinemia			Chi-Squared Test	
	Present	Absent	Total	$\chi 2$	P Value
Present	9 (47.4%)	10 (52.6%)	19 (100.0%)	0.332	0.564
Absent	17 (39.5%)	26 (60.5%)	43 (100.0%)		
Total	26 (41.9%)	36 (58.1%)	62 (100.0%)		

Chi-squared test was used to explore the association between 'Hyperhomocysteinemia' and 'DM'. There was no significant difference between the various groups in terms of distribution of Hyperhomocysteinemia ($\chi 2$ = 0.332, p = 0.564).

47.4% of the participants in the group [DM: Present] had [Hyperhomocysteinemia: Present]. 39.5% of the participants in the group [DM: Absent] had [Hyperhomocysteinemia: Present]. 52.6% of the participants in the group [DM: Present] had [Hyperhomocysteinemia: Absent]. 60.5% of the participants in the group [DM: Absent] had [Hyperhomocysteinemia: Absent].



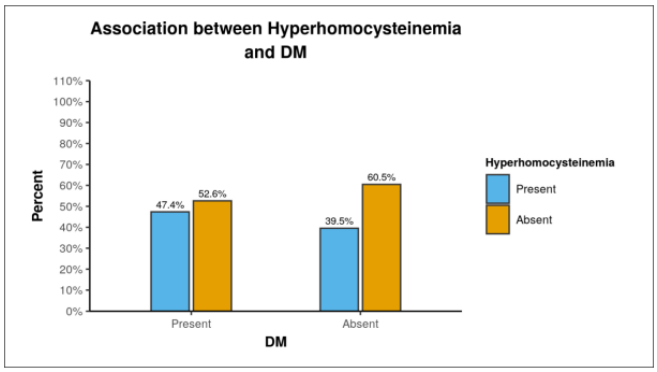


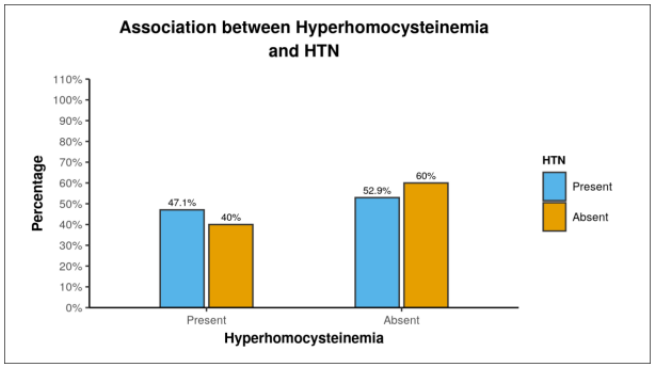
Table 12: Odds Ratios and Relative Risks

Predictor/Risk Factor	Outcome	Odds Ratio (95% CI)	Relative Risk (95% CI)
DM: Present	Hyperhomocysteinemia: Present	1.38 (0.46-4.09)	1.2 (0.63-2.11)
DM: Present	Hyperhomocysteinemia: Absent	0.73 (0.24-2.16)	0.87 (0.5-1.35)
DM: Absent	Hyperhomocysteinemia: Present	0.73 (0.24-2.16)	0.83 (0.47-1.59)
DM: Absent	Hyperhomocysteinemia: Absent	1.38 (0.46-4.09)	1.15 (0.74-1.99)
Hyperhomocysteinemia: Present	DM: Present	1.38 (0.46-4.09)	1.25 (0.59-2.58)
Hyperhomocysteinemia: Present	DM: Absent	0.73 (0.24-2.16)	0.91 (0.62-1.27)
Hyperhomocysteinemia: Absent	DM: Present	0.73 (0.24-2.16)	0.8 (0.39-1.69)
Hyperhomocysteinemia: Absent	DM: Absent	1.38 (0.46-4.09)	1.1 (0.79-1.63)

Table 13: Association between Hyperhomocysteinemia and HTN (n = 62)

HTN	Hyperhomocysteinemia			Chi-Squared Test	
	Present	Absent	Total	$\chi 2$	P Value
Present	8 (47.1%)	9 (52.9%)	17 (100.0%)	0.252	0.615
Absent	18 (40.0%)	27 (60.0%)	45 (100.0%)		
Total	26 (41.9%)	36 (58.1%)	62 (100.0%)		

Chi-squared test was used to explore the association between 'Hyperhomocysteinemia' and 'HTN'. There was no significant difference between the various groups in terms of distribution of Hyperhomocysteinemia ($\chi 2$ = 0.252, p = 0.615). 47.1% of the participants in the group [HTN: Present] had [Hyperhomocysteinemia: Present]. 40.0% of the participants in the group [HTN: Absent] had [Hyperhomocysteinemia: Present]. 52.9% of the participants in the group [HTN: Present] had [Hyperhomocysteinemia: Absent]. 60.0% of the participants in the group [HTN: Absent] had [Hyperhomocysteinemia: Absent].



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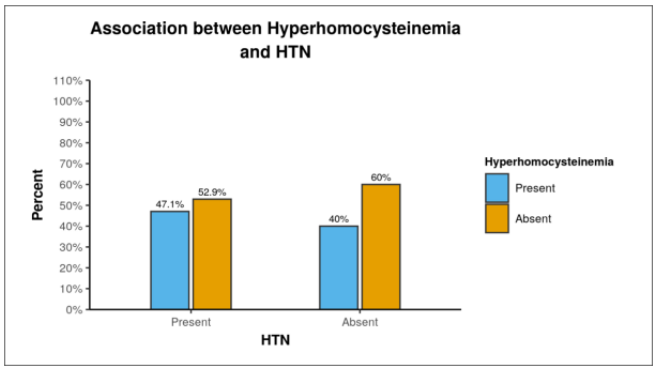


Table 14: Odds Ratios and Relative Risks

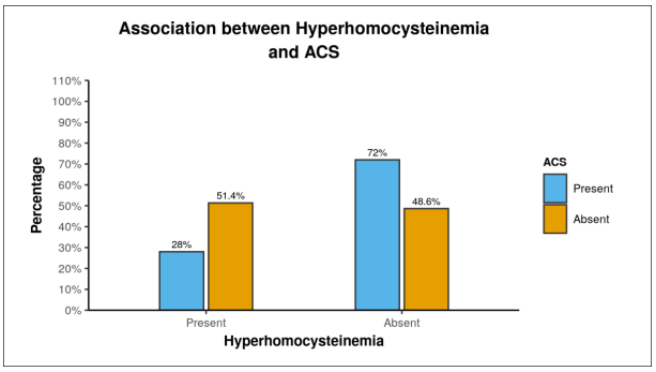
Predictor/Risk Factor	Outcome	Odds Ratio (95% CI)	Relative Risk (95% CI)
HTN: Present	Hyperhomocysteinemia: Present	1.33 (0.43-4.1)	1.18 (0.6-2.08)
HTN: Present	Hyperhomocysteinemia: Absent	0.75 (0.24-2.31)	0.88 (0.5-1.38)
HTN: Absent	Hyperhomocysteinemia: Present	0.75 (0.24-2.31)	0.85 (0.48-1.66)
HTN: Absent	Hyperhomocysteinemia: Absent	1.33 (0.43-4.1)	1.13 (0.73-2.02)
Hyperhomocysteinemia: Present	HTN: Present	1.33 (0.43-4.1)	1.23 (0.55-2.7)
Hyperhomocysteinemia: Present	HTN: Absent	0.75 (0.24-2.31)	0.92 (0.64-1.26)
Hyperhomocysteinemia: Absent	HTN: Present	0.75 (0.24-2.31)	0.81 (0.37-1.82)
Hyperhomocysteinemia: Absent	HTN: Absent	1.33 (0.43-4.1)	1.08 (0.79-1.55)

Table 15: Association between Hyperhomocysteinemia and NSTEMI/ACS (n = 62)

ACS	Hyperhomocysteinemia			Chi-Squared Test	
	Present	Absent	Total	$\chi 2$	P Value
Present	7 (28.0%)	18 (72.0%)	25 (100.0%)	3.341	0.068
Absent	19 (51.4%)	18 (48.6%)	37 (100.0%)		
Total	26 (41.9%)	36 (58.1%)	62 (100.0%)		

Chi-squared test was used to explore the association between 'Hyperhomocysteinemia' and 'ACS'.

There was no significant difference between the various groups in terms of distribution of Hyperhomocysteinemia ($\chi 2$ = 3.341, p = 0.068). 28.0% of the participants in the group [ACS: Present] had [Hyperhomocysteinemia: Present]. 51.4% of the participants in the group [ACS: Absent] had [Hyperhomocysteinemia: Present]. 72.0% of the participants in the group [ACS: Present] had [Hyperhomocysteinemia: Absent]. 48.6% of the participants in the group [ACS: Absent] had [Hyperhomocysteinemia: Absent].



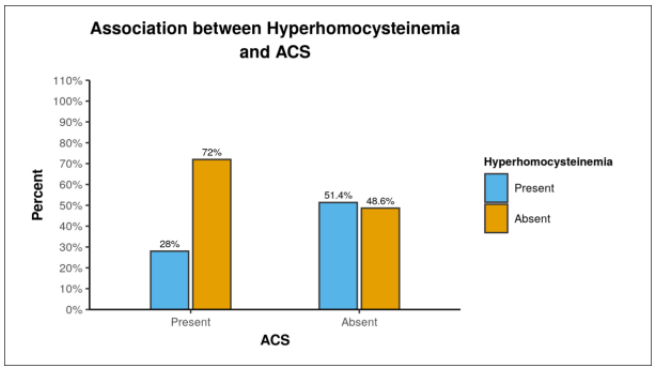


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Table 16: Odds Ratios and Relative Risks

Predictor/Risk Factor	Outcome	Odds Ratio (95% CI)	Relative Risk (95% CI)
ACS: Present	Hyperhomocysteinemia: Present	0.37 (0.12-1.09)	0.55 (0.26-1.04)
ACS: Present	Hyperhomocysteinemia: Absent	2.71 (0.92-8.03)	1.48 (0.97-2.27)
ACS: Absent	Hyperhomocysteinemia: Present	2.71 (0.92-8.03)	1.83 (0.96-3.81)
ACS: Absent	Hyperhomocysteinemia: Absent	0.37 (0.12-1.09)	0.68 (0.44-1.03)
Hyperhomocysteinemia: Present	ACS: Present	0.37 (0.12-1.09)	0.54 (0.26-1.04)
Hyperhomocysteinemia: Present	ACS: Absent	2.71 (0.92-8.03)	1.46 (0.97-2.22)
Hyperhomocysteinemia: Absent	ACS: Present	2.71 (0.92-8.03)	1.86 (0.96-3.88)
Hyperhomocysteinemia: Absent	ACS: Absent	0.37 (0.12-1.09)	0.68 (0.45-1.03)

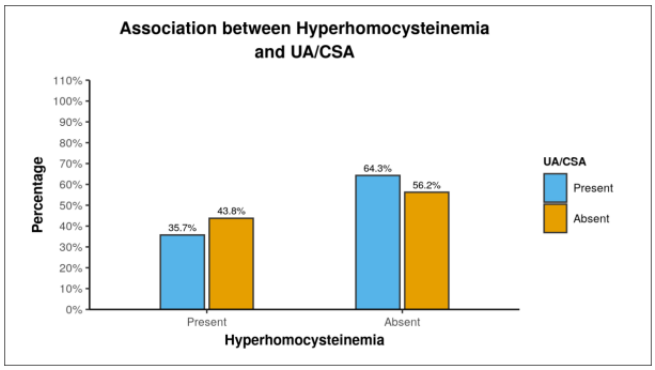
Table 17: Association between Hyperhomocysteinemia and UA/CSA (n = 62)

UA/CSA	Hyperhomocysteinemia			Chi-Squared Test	
	Present	Absent	Total	$\chi 2$	P Value
Present	5 (35.7%)	9 (64.3%)	14 (100.0%)	0.287	0.592
Absent	21 (43.8%)	27 (56.2%)	48 (100.0%)		
Total	26 (41.9%)	36 (58.1%)	62 (100.0%)		

Chi-squared test was used to explore the association between 'Hyperhomocysteinemia' and 'UA/CSA'.

There was no significant difference between the various groups in terms of distribution of Hyperhomocysteinemia ($\chi 2 = 0.287$, $p = 0.592$).

35.7% of the participants in the group [UA/CSA: Present] had [Hyperhomocysteinemia: Present]. 43.8% of the participants in the group [UA/CSA: Absent] had [Hyperhomocysteinemia: Present]. 64.3% of the participants in the group [UA/CSA: Present] had [Hyperhomocysteinemia: Absent]. 56.2% of the participants in the group [UA/CSA: Absent] had [Hyperhomocysteinemia: Absent].



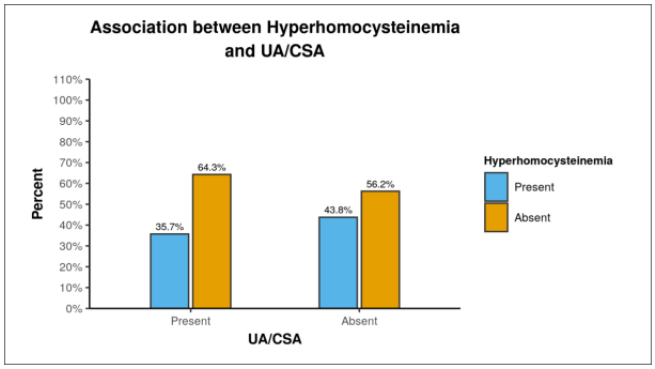


Table 18: Odds Ratios and Relative Risks

Predictor/Risk Factor	Outcome	Odds Ratio (95% CI)	Relative Risk (95% CI)
UA/CSA: Present	Hyperhomocysteinemia: Present	0.71 (0.21-2.45)	0.82 (0.35-1.59)
UA/CSA: Present	Hyperhomocysteinemia: Absent	1.4 (0.41-4.8)	1.14 (0.66-1.72)
UA/CSA: Absent	Hyperhomocysteinemia: Present	1.4 (0.41-4.8)	1.22 (0.63-2.82)
UA/CSA: Absent	Hyperhomocysteinemia: Absent	0.71 (0.21-2.45)	0.87 (0.58-1.52)
Hyperhomocysteinemia: Present	UA/CSA: Present	0.71 (0.21-2.45)	0.77 (0.29-1.92)
Hyperhomocysteinemia: Present	UA/CSA: Absent	1.4 (0.41-4.8)	1.08 (0.8-1.42)
Hyperhomocysteinemia: Absent	UA/CSA: Present	1.4 (0.41-4.8)	1.3 (0.52-3.4)
Hyperhomocysteinemia: Absent	UA/CSA: Absent	0.71 (0.21-2.45)	0.93 (0.7-1.25)

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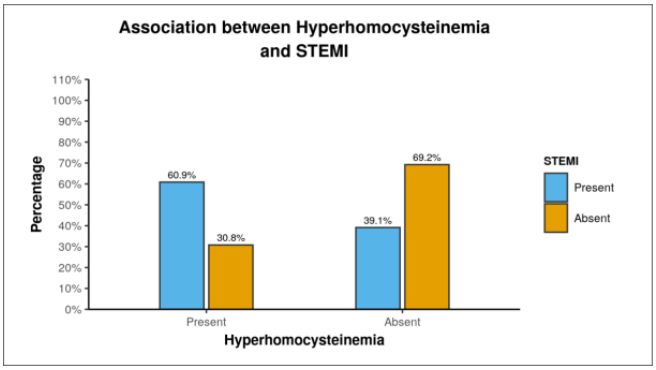
Table 19: Association between Hyperhomocysteinemia and STEMI (n = 62)

STEMI	Hyperhomocysteinemia			Chi-Squared Test	
	Present	Absent	Total	$\chi 2$	P Value
Present	14 (60.9%)	9 (39.1%)	23 (100.0%)	5.383	0.020
Absent	12 (30.8%)	27 (69.2%)	39 (100.0%)		
Total	26 (41.9%)	36 (58.1%)	62 (100.0%)		

Chi-squared test was used to explore the association between 'Hyperhomocysteinemia' and 'STEMI'. There was a significant difference between the various groups in terms of distribution of Hyperhomocysteinemia ($\chi 2$ = 5.383, p = 0.020).

60.9% of the participants in the group [STEMI: Present] had [Hyperhomocysteinemia: Present]. 30.8% of the participants in the group [STEMI: Absent] had [Hyperhomocysteinemia: Present]. 39.1% of the participants in the group [STEMI: Present] had [Hyperhomocysteinemia: Absent]. 69.2% of the participants in the group [STEMI: Absent] had [Hyperhomocysteinemia: Absent].

Participants in the group STEMI: Present had the larger largest proportion of Hyperhomocysteinemia: Present. Participants in the group STEMI: Absent had the larger largest proportion of Hyperhomocysteinemia: Absent.



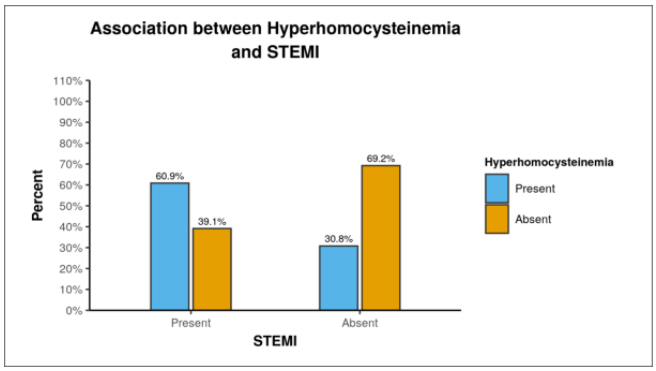


Table 20: Odds Ratios and Relative Risks

Predictor/Risk Factor	Outcome	Odds Ratio (95% CI)	Relative Risk (95% CI)
STEMI: Present	Hyperhomocysteinemia: Present	3.5 (1.19-10.29)	1.98 (1.11-3.53)
STEMI: Present	Hyperhomocysteinemia: Absent	0.29 (0.1-0.84)	0.57 (0.31-0.92)
STEMI: Absent	Hyperhomocysteinemia: Present	0.29 (0.1-0.84)	0.51 (0.28-0.9)
STEMI: Absent	Hyperhomocysteinemia: Absent	3.5 (1.19-10.29)	1.77 (1.08-3.22)
Hyperhomocysteinemia: Present	STEMI: Present	3.5 (1.19-10.29)	2.15 (1.12-4.23)
Hyperhomocysteinemia: Present	STEMI: Absent	0.29 (0.1-0.84)	0.62 (0.37-0.93)
Hyperhomocysteinemia: Absent	STEMI: Present	0.29 (0.1-0.84)	0.46 (0.24-0.89)
Hyperhomocysteinemia: Absent	STEMI: Absent	3.5 (1.19-10.29)	1.62 (1.07-2.68)

Literature Review

The usual risk factors for coronary artery disease mainly include hypertension, hyperlipidemia and diabetes, smoking and family history. Still it is believed that there can be some new potentially reversible risk factors for CAD. The eminent concentration of the amino acid homocysteine in blood is one such factor.

Studies of homocysteine and CAD were acknowledged from a English-language literature namely, MEDLINE from January 1976 to January 1999 where it has been discussed and revealed about 17 retrospective (cross-sectional, case control) studies. (Wilcken, 1976; Israelsson et al., 1988; Malinow et al., 1990; Ubbink et al., 1991; Dudman et al., 1993; Wu et al., 1994; Graham et al., 1997), one meta analysis (according to studies completed before 1995) and eight potential studies supporting the theory of tHcy as a risk factor for CAD. (Boushey et al., 1995; Wald et al., 1998; Bots et al., 1999)

Dietary proteins like yellow and green leafy vegetables, poultry products, grains and meats contain sulfur methionine and the metabolism of this element leads to the formation of Homocysteine (amino acid). The overview of Hcy metabolism is presented in (Figure 1). (Finkelstein, 1990) It has been revealed that many diseases and medications are there which elevate Hcy levels and that elevation could lead to CAD (Table 1). Not only that it has also been examined and ravelled that Hcy increase the risk of CAD through toxic modification to endothelial cells, increase in coagulation property, moderate triglyceride levels production of oxygen free radical which leads to lower endothelial reactivity with incentive cell proliferation of smooth muscle. (Tawakol et al., 1997) It has been proven that vegetarians are more prone to risk for hyperhomocysteinemia due to low levels of B12. (Herrmann et al., 2003; Bissoli et al., 2002) It seems that coffee consumption linked with moderate elevation levels of homocysteine. Various epidemiological studies have found a relation between homocysteine

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concentration with plasma folate levels and with vitamin B12 and B16 levels as well. It has been resulted and proven that intake of folic acid supplements daily reduces the levels of homocysteine which in regards turn down the risk of CAD. (Mizrahi et al., 2003)

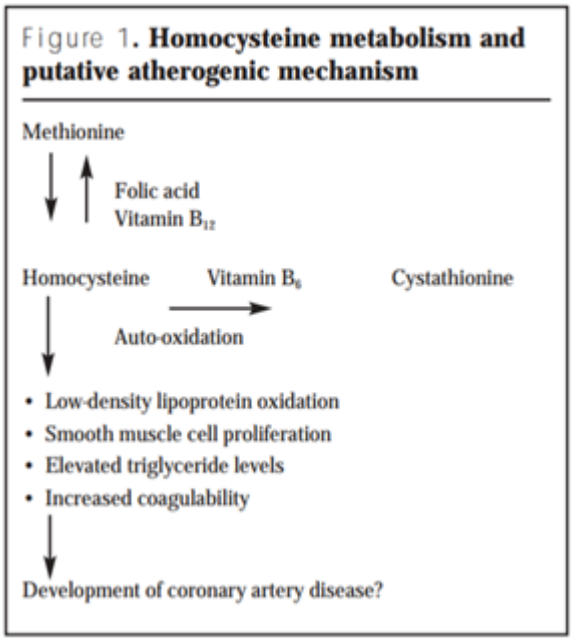

Figure 1: Homocysteine Metabolism and Putative Atherogenic Mechanism

Table 1. **Causes of hyperhomocysteinemia**

NUTRITION
Deficiencies in folic acid, vitamin B_6, and vitamin B_{12}
DISEASE STATES
Chronic renal failure
Hypothyroidism
Malignancies (all, especially breast, ovarian, pancreatic)
Pernicious anemia
Systemic lupus erythematosus
DRUGS
Cigarettes
Antimetabolites (eg, methotrexate)
Anticonvulsants (eg, phenytoin, carbamazepine)
Cholestyramine
Nicotinic acid
Nitrous oxide
Thiazide diuretics
GENETIC DEFICIENCIES
Cystathionine β-synthase
Methionine synthase
Methylenetetrahydrofolate reductase

Table 1: Cause of Hyperhomocysteinemia

Evidence has been found which indicates Hcy is an independent risk factor for CAD. The Meta analysis of 27 observational studies from 1976 to 1999 concluded that 10% of the United States population's CAD risk depends upon the elevated level of Hcy. The ration for CAD of a 5-µmol/L tHcy was 1.6 for men and for women 1.8. The study concluded that 5-µmol/L increase of Hcy raises the risk of CDA as much as a 5-µmol/L increase in cholesterol. In the summary of the study it was determined that homocysteine as a risk factor for CAD according to the Meta analysis was 1.7. (Boushey et al., 1995) Another eight potential group of studies have explained positive association between elevated Hcy concentration and risk of CAD statistically. (Nygård et al., 1997) One of the studies has been declared that relative risk factor of 1.41 for every 4-µmol/L increase of Hcy. The study by Nygard et al. showed a strong relation between Hcy concentration and overall mortality by following and examined heart disease patients for 4.6 years. (Nygård et al., 1997) It has been concluded that the Hcy levels above 15 µmol/L and with an moderate morality or 1.6 for those patients who have tHcy concentration of 15 µmol/L in comparison with patients with concentration levels of 10 µmol/L can show a strongest association with CAD.

In this study a survey has been done among 62 people (patients) of different age groups, different sex, and patient with diabetes mellitus, patient with hypertension, CAD with unstable angina or UA and CAD with chronic stable angina or CSA, patient with Non ST-Elevation Myocardial Infarction (ACS/NSTEMI) and ST-Elevation Myocardial Infarction (STEMS) in MGM Hospital, Aurangabad.

Patients with homocysteine level > 15 µmol/L are considered to have hyperhomocystenemia.

The medical study involves different kinds of diagnosis to find the reason for CAD but here the process "Cardiac catheterization and Angiogram" can show the reason of CAD as well as can represent the importance of this research work. In cardiac catheterization the doctor generally inserts a catheter into an artery or vein very gently which reaches up to the heart. To guide the catheter to the proper position X-rays are used. As blood vessels cannot be visible in an X-ray so to identify arteries and veins a dye used to add into the bloodstream. If the patient has a blockage in the artery or Atherosclerosis then it requires a treatment where balloons is used to push through the catheter and by inflating it try to improve the issue and as a result the blood can flow easily in the coronary arteries.

Drugs play an important role in the treatment of CAD and to prevent the complications related to it. According to medical studies, medication can treat the treat of CAD if the blockage of the artery is less than 70%. The usual symptom of CAD is chest pain and to prevent it a drug namely nitrates used to prescribe to reduce the pain. A type of nitrate, Nitroglycerin dilates the blood vessels and helps the heart to pump blood effortlessly for which the patient gets relief from chest pain. Another drug which is also often prescribed to treat chest pain is Beta-blockers.

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This drug used to lower the blood pressure of the patient by slowing down the heart rate. Eventually this drug decreases the amount of oxygen that the patient's heart needs to work and leads to the reduction of chest pain. Blood clots block the path of blood flow and which ultimately leads to heart attack. So to prevent CAD and heart attacks certain drugs are there which make it hard for the blood to form clots in the arteries and reduce the risk of attack. Some of those medicines are aspirin, clopidogrel (Plavix), eptifibatide (Integrilin) and ticlopidine (Ticlid).

Conclusion

The study concludes that many patients with Coronary Artery Disease hashyperhomocystenemia. Significant association was not found in patients having Diabetes Mellitus and Hypertension, but was significantly associated with patients who presented with acute ST Elevation Myocardial Infarction.
Some of the drawbacks of this study

1) The study was done in 1 centre only.
2) Small sample size.
3) Bias

Recommendations

From all the published literature and reviews it can be concluded that homocysteine is an independent risk factor for coronary artery disease and it shares a strong association in-between. Though some of the studies supported that through some minimal medication, proper diet and regular exercise a person can control the risk of CAD. In this study the survey of 62 patients with different characteristics, different symptoms and different sex etc. shown increase in homosysteine level which indicates the risk towards CAD. So from this it is easy to get to the conclusion that the association of Hyperhomocysteinemia in patients with Coronary Artery Disease is significant.

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