https://doi.org/ 10.48047/AFJBS.6.7.2024.1669-1679

Vitamin B_{12} Deficiency Induced Hyperhomocysteinemia Leading to Myocardial Infarction

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Article History

Volume 6,Issue 7, 2024

Received: 29 Mar 2024

Accepted : 22 May 2024

doi: 10.48047/AF5BS.6.7. 2024. 1669-1679

Abstract

Vitamin B_{12} is a red colored, heat stable, water-soluble vitamin also called as Cobalamin or extrinsic factor of Castle. It contains only a single cobalt atom which is 4.35% by weight. It is absorbed in our body in ileum in presence of two factors intrinsic factor of Castle and cobalophilin. To find out the levels of homocysteine, vitamin B_{12} and folate in serum samples of patients of myocardial infarction and healthy control. To find association between hyperhomocysteinemia and Myocardial infarction. This study was carried out in our tertiary care hospital for a period of 2 months from 16 June 2022 to 14 August 2022. Study included 97 diagnosed cases with Myocardial Infarction (coronary artery disease). The diagnosis of Myocardial Infarction was made by Electrocardiograph (ECG) and serum levels of troponin I and Creatinine kinase-MB(CK-MB). The blood samples were taken from patients for conducting the study before angiography or before starting thrombolytics. Most of the cases taken up for project belonged to age group between 40-70 yrs, with maximum of 81 yrs and minimum age being 32 yrs. We also took samples of 50 random normal age matched control who were healthy people from the society. Most of them were from age group between 4060 yrs. The serum was separated and analysed for vitamin B_{12} and folic acid levels using competitive binding receptor assay and competitive binding immuneenzymatic assay respectively. Plasma was analysed for total homocysteine using a chemiluminescent micro particle immunoassay on auto analysers in biochemistry section of the central laboratory. In this study a negative correlation could be established between hyperhomocysteinemia and vitamin B_{12} deficiency and positive correlation was seen in between patients with hyperhomocysteinemia and myocardial infarction.

Keywords: Vitamin deficiency, Myocardial infarction, hyperhomocysteinemia, Blood plasma.

INTRODUCTION

Vitamin B_{12} is a red colored, heat stable, water-soluble vitamin also called as Cobalamin or extrinsic factor of Castle. It contains only a single cobalt atom which is 4.35% by weight. There are four pyrrole rings which coordinate with a cobalt atom to form a corrin ring. It is absorbed in our body in ileum in presence of two factors intrinsic factor of Castle and cobalophilin. The main transport form of vitamin B_{12} in blood is predominantly methyl cobalamin. Transcobalamin is a glycoprotein which acts as specific carrier for vitamin B_{12}. The storage form of vitamin B_{12} found in liver is Ado-cobalamin with trans Corrin. The best source of vitamin B_{12} is liver besides dairy products specially curd (1).

Homocysteine methyl transferase (an enzyme required for conversion of homocysteine to methionine) requires methyl cobalamin for its activity. This methyl group of cobalamin is derived from the methyl tetra hydro folate (THFA), which is obtained during regeneration of free THFA. In case of Vitamin B_{12} deficiency regeneration of THFA is not possible leading to trapping of folate in methyl form causing non-availability of folic acid. Vitamin B_{12} deficiency is also associated with non-conversion of homocysteine to methionine leading to hyperhomocysteinemia. Hyperhomocysteinemia is defined as a medical condition characterized by levels of homocysteine above 15 micromol per liters (2,3).

There can be genetic mutation in enzymes like methionine synthase, THFA reductase etc. resulting in hyperhomocysteinemia. Environmental factors and nutritional deficiencies are also responsible. Plasma levels of homocysteine above the level of 15 µmol/L is known as risk factor of coronary artery disease which could lead to myocardial infarction. Since kidney is mainly responsible for the clearance of homocysteine from plasma therefore in case of renal failure also hyperhomocysteinemia can occur due to defective clearance by kidney (4).

The cardiovascular complications due to homocystinuria are as a result of its effects on smooth muscle cells of vessels and its endothelium. This causes functional and structural alterations in the vessels wall leading to endothelial cell vandalization, reducing pliability of vessels, and altering the process of haemostasis (5).

Coronary artery disease due to decreased oxygen and nutrient provision to heart is responsible for 1/3 rd of all cardiovascular diseases. A number of studies have come up with results which indicate moderate to severe levels of blood homocysteine to be responsible for cardiovascular disease (6,7).

In a country like India where nearly 40% people are vegetarians including vegans as well as millions below poverty line who cannot afford two square meals, it becomes a hotspot for vitamin deficiency which might lead to hyperhomocysteinemia which in turn could lead to cardiovascular complications. Vitamin B_{12} deficiency could be found in either vegans or in poor people who cannot afford dairy products and non-vegetarian items, which are one of the good sources of vitamin B_{12} (5).

homocysteine which in turn declines the morbidity of CAD (27,28,29). Thus, providing adequate doses of pyridoxine, B_{12} and folic acid may lower the homocysteine levels.

OBJECTIVES

1. To find out the levels of homocysteine, vitamin B_{12} and folate in serum samples of patients of myocardial infarction and healthy control.
2. To find association between hyperhomocysteinemia and Myocardial infarction.

MATERIAL AND METHODS

It was an observational study conducted over two months from 16 June 2022 to 14 August 2022 tertiary care hospital in North India.

Study design – Prospective observational case-control study

Sample size- 97 Myocardial Infarction cases who were hospitalized and 50 healthy agematched controls.

Duration of study- 2 months.

METHODS

Venous blood sample was obtained from both cases and controls. A total 97 cases and 50 controls were included in this study. Cases were patients with Myocardial Infarction admitted in cardiac care unit of the tertiary care centre and controls were healthy individuals from society in the same age group as cases. The serum was separated and analysed for vitamin B_{12} and folic acid levels using competitive binding receptor assay and competitive binding immuneenzymatic assay respectively. Plasma was analysed for total homocysteine using a chemiluminescent micro particle immunoassay on auto analysers in biochemistry section of the central laboratory (30).

Inclusion criteria

All the patients of Myocardial Infarction admitted in the hospital.

Exclusion criteria

a. Patients of MI who were given thrombolytic.
b. Patients of MI who underwent angiography.

Statistical Analysis

Data was analysed with SPSS (Statistical Package for Social Sciences) version 23. Results were expressed as mean, S.D. and 95% confidence Internal. Quantitative data without a normal distribution were analysed using non parametric tests and data with normal distribution were analysed using the parametric tests.

Prior to start of the study clearance for the project was obtained from both ethical and research committee vide letter No. E-1/2022/238 dated 4/06/22.Informed and written consent was also taken from patients for their participation in the project.

OBSERVATION AND RESULTS

Certain observatory studies and procedures were followed and performed to access the knowledge and information about the diseased state and health state distinction.

Table 1. Depicting association between gender and myocardial infarction

Gender	**Group**		**chi-square, p-value**
	cases	**controls**	
Female	20	29	20.75, <0.001
Male	77	21	

This table 1 shows the gender composition of cases of Myocardial Infarction. In table we can see greater number of males in cases indicating more prevalence of myocardial infarction in males than females.

Table 2. Depicting common characteristics in cases

Common characteristics	**Prevalence**	**N**	**Percentage**
Diabetes Mellitus	31	97	31.95
Hypertension	40	97	41.23
Alcoholic	26	97	26.80
Smoking	48	97	49.48
Vegetarians	40	97	41.23

This table 2 depicts that almost fifty percent of the cases are smokers and more than forty percent of the cases with Myocardial Infarction are hypertensive and vegetarians

Table3. Depicting levels of homocysteine in male and female patients of myocardial Infarction

Homocysteine levels	Female	Male	Total
Above15 µmol/l	8	36	44
Below 15 µmol/l	12	41	53

This table 3 shows the homocysteine levels in males and females separately in cases. According to table we conclude the prevalence of hyperhomocysteinemia is significant among cases and that too specially in males.

Table 4. Depicting correlation between vitamin B12 and homocysteine in cases and control Separately

Category	N	Correlation coefficient	P value
Cases	97	-0.416	0.00
Control	50	-0.802	0.00

This table clearly depicts in cases (N=97) a moderately negative correlation between vitamin B12 and homocysteine indicated by a correlation coefficient of -0.416 and P value which is 0.00 while in controls (N=50) a strong negative correlation is indicated by a correlation coefficient of -0.802 and P value which is 0.00. The P value here indicates that the correlation is significant.

Table 5. Depicting correlation between folic acid and homocysteine in cases and control

Category	N	Correlation coefficient	P value

Cases	97	-0.135	0.00
Control	50	-0.796	0.00

Table 5 depicts the correlation between folic acid and homocysteine in cases (N=97) which is mild negative indicated by correlation coefficient of -0.135 and P value 0 .00. In controls (N=50) the strong negative correlation is indicated by correlation coefficient of -0.796 and P value 0.00. The P value here indicates that correlation is significant.

A total of 97 patients with myocardial infarction who were admitted in the tertiary care hospital were included in the study, out of 97 patients 48 (49.48%) were smokes and 40 (41.23%) were vegetarians. On taking history and clinical examination 40 (41.23%) were found to be hypertensive as seen in table 2.

Out of 97 cases of Myocardial Infarction, 44 patients had hyperhomocysteinemia. More number of male (n=36) were found to have higher serum homocysteine levels as compared to females (n=08) as is represented in table 3. Thirty patients with hyperhomocysteinemia also had vitamin B_{12} deficiency which shows a significant inverse correlation as depicted in table number 4. Even serum folic acid levels were low in 35 cases (36.08%) as compared to controls (n=5, 10%) although this shows a weak negative correlation on regression analysis (Table 5).

DISCUSSION

This study was carried out in our tertiary care hospital for a period of 2 months from 16 June 2022 to 14 August 2022. Study included 97 diagnosed cases with Myocardial Infarction (coronary artery disease). The diagnosis of Myocardial Infarction was made by Electrocardiograph (ECG) and serum levels of troponin I and Creatinine kinase-MB(CK-MB). The blood samples were taken from patients for conducting the study before angiography or before starting thrombolytics. Most of the cases taken up for project belonged to age group between 40-70 yrs, with maximum of 81 yrs and minimum age being 32 yrs. We also took samples of 50 random normal age matched control who were healthy people from the society. Most of them were from age group between 40-60 yrs. Before taking samples for the study, a written informed consent and a brief history was taken. History included personal history and family history which included the history of signs and symptoms for the illness, for diabetes mellitus (DM), hypertension (HTN), alcoholism, smoking and substance abuse. Keeping in mind the prevalence of Vitamin B12 deficiency among vegetarians, history related to their eating preferences (non- vegetarian or vegetarian) was also taken along with that regarding vitamins supplements intake. History was taken with utmost cautiousness and efforts were put to obtain history from each and every patient. On analysis we found High prevalence of vitamin B_{12} deficiency in control population which was unexpected (21 out of 50 i.e., nearly 42%), which might be result of nutritional deficiency due to maximum number of people being vegetarians in diet. Pernicious anemia does not seem to be a cause being uncommon in India.

However, the antibody against Intrinsic factor could not be assayed to confirm the same. In our analysis to check for the association between gender and prevalence of myocardial Infarction we found that out of 97 cases (N=97), there were 20 females(20.61 %) who were diagnosed with Myocardial Infarction and 77 males (79.38%) who were diagnosed with same , indicating a strong association between the male gender and prevalence of Myocardial Infarction , which is the similar to results found in the study by M P Iqbal et al, where out of 224 cases of myocardial infarction 169 (75.44%)were males and 55 (24.55%) were females (31).

Out of 44 cases with hyperhomocysteinemia, 23 cases (23.71% of total cases) were chronic smokers also 21 (21.64% of total cases) were vegetarians. However, in patients with hyperhomocysteinemia and vitamin B_{12} deficiency (n=30, 30.92 % of total cases), nearly 15 patients were reported to be vegetarians. In a study done by Bissoli L et al homocysteine was significantly higher in vegetarian subjects than in controls (23.9 +/- 21.3 vs. 11.6 +/- 4.9 micromol/L, $p < 0.001$). Serum vitamin B_{12} levels were lower in vegetarian patients as compared to control subjects (171.2 +/- 73.6 vs. 265.0 +/- 52.2 pmol/L, $p < 0.01$; normal range 220-740 pmol/L). In vegetarian subjects, significant inverse correlations were found between total homocysteine and serum vitamin B_{12} levels ($r=-0.776$, $p< 0.001$) and between total homocysteine and serum folate levels ($r=-0.340$, $p< 0.05$). This is in accordance with our study except we could not establish a strong negative correlation between homocysteine and folate levels (32).

Data was analysed for finding association between the prevalence of hyperhomocysteinemia and myocardial infarction. Out of 97 cases, 44 cases of myocardial Infarction were found to have serum homocysteine levels more than 15 µmol/L(hyperhomocysteinemia) while 53 cases (54.64%) of myocardial Infarction were found to have normal serum homocysteine levels (45.36%, p value <0.001) indicating a strong association between hyperhomocysteinemia and myocardial infarction. While MP Iqbal et al reported a higher mean of homocysteine levels in MI cases (18+/-8.36 micromol/L) as compared to mean levels in controls (16.4+/-4.9 micromol/L), Although this was not significant. This level is highest for Indian population which was observed in their study for normal healthy individuals when compared to healthy individuals from other countries. The etiology is not known (31). Our results were in line with study done by Cristina Nedelcu et al. which showed a significant (P<0.001) risk for MI in patients with a high fasting plasma homocysteine level (OR, 11.822; 95% CI=3.425-40.802) (33).

We also checked the data for corelation between vitamin B_{12} and homocysteine and we found a (correlation coefficient of -0.416 and p value <0.001) strong association and moderately negative corelation between vitamin B_{12} and homocysteine. On subjecting data to regression analysis, serum homocysteine was observed to possess an inverse correlation with serum level of Vitamin B_{12}, in general. This inverse correlation ($P = 0.005$, $r2 = 0.052$) between serum level of Vitamin B_{12} and serum level of homocysteine was statistically significant as reported by Sunil et al (34). In study by MP Iqbal et al a significant correlation was observed when homocysteine values were compared between vitamin B12 deficient cases and vitamin B12 controls (p value 0.0001) (31).

Also, in our study we found that 45 cases (46.39% of total cases) were deficient in vitamin B_{12} out of which around 30 cases were found to have hyperhomocysteinemia as well. That is nearly 67% of the patients having cardiovascular manifestation were having hyperhomocysteinemia along with vitamin B_{12} deficiency, indicating a strong correlation between serum homocysteine and vitamin B_{12} levels. These are quite in line with results of the study done by Brian M Gilfix

where he showed the sensitivity of homocysteine for identifying vitamin B_{12} deficiency to be more than 95%(35).

A weakly negative correlation (corelation coefficient of -0.135 and p value of 0.188) was found between serum folate and homocysteine levels, showing hike in homocysteine levels with drop in folic acid levels which is similar to the study done by Moninder et al (36). Our study also showed a significantly high value of homocysteine in patients with folate deficiency (p value =0.0001 i.e. <0.001) which are in lines with study done by M.P. Iqbal et al (p value<0.001%) (31).

SUMMARY

It was a study that involved the patients of myocardial infarction which were diagnosed by ECG findings as well as troponin I and CK-MB levels in serum. A total of 97 cases were taken for the study which included both males and females mostly in age group between 50-70 yrs. A written informed consent was taken from patients before taking samples. Along with fasting venous blood samples, a brief history was also taken. Blood samples were sent for laboratory diagnosis for calculating serum homocysteine, vitamin B_{12} and folic acid levels. Around 50 age matched healthy controls were also included in study who mostly belonged to 40-70 yrs of age group. After calculation of levels of various parameters required for our study, data was used for statistical analysis using SPSS software. From the analysis various association and correlations were derived. An association between male gender and myocardial infarction was observed in our study (79.38% in males) A negative correlation between Vitamin B12 and homocysteine and between Folic acid and homocysteine was observed. Preponderance was seen among males for hyperhomocysteinemia, as well as number of cases having deficiency of Vitamin B12 and Folic acid. On observation we concluded that there exists a moderate negative corelation between Vitamin B_{12} and homocysteine in cases. Similarly while finding correlation between folic acid and homocysteine, we concluded that their exists weak negative correlation in cases .Study was conducted in a population which seemed overall nutritionally deficient as some controls too had low serum folic acid and vitamin B_{12} levels but the negative correlation between hyperhomocysteinemia and vitaminB_{12} in patients of myocardial infarction was observed thus establishing the role of hyperhomocysteinemia causing M.I. in vitamin B_{12} deficient persons.

CONCLUSION

In this study a negative correlation could be established between hyperhomocysteinemia and vitamin B_{12} deficiency and a positive correlation was seen in between patients with hyperhomocysteinemia and myocardial infarction. Steinemia, vitamin B12 deficiency, and myocardial infarction. The negative correlation observed between hyperhomocysteinemia and vitamin B12 deficiency suggests a potential interplay between these factors in cardiovascular health. Moreover, the positive correlation between hyperhomocysteinemia and myocardial infarction highlights the significance of addressing elevated homocysteine levels as a potential risk factor for cardiac events. These insights underscore the importance of further research to elucidate the mechanisms underlying these associations and inform targeted interventions aimed at reducing the burden of myocardial infarction.

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