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Estimation of Homocysteine and its Relationship with Vitamin B_{12} and Folic Acid Levels in Patients with Cardiovascular Disease

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Abstract*— Globally, one of the leading causes of death is cardiovascular disease (CVD). The plasma levels of homocysteine rise after myocardial ischemia and are involved in numerous methylation processes. This study aimed to evaluate homocysteine levels and their relationship with vitamin B_{12} and folic acid (vitamin B_9) in patients with cardiovascular disease and early-stage heart disease due to hypertension, lipidemia, etc. The present study included 120 participants aged between 30 to 70 years and was divided into three groups. Forty patients with acute myocardial infarction (G1), forty patients with early-stage heart disease (G2), and forty healthy participants (G3). Quantitative determination of homocysteine, vitamin B_{12}, and vitamin B_9 is measured based on the competitive enzyme-linked immunosorbent assay (ELISA) technology. Acute myocardial infarction and early-stage heart disease patients also had their total cholesterol, triglyceride, HDL, and LDL levels examined. The study showed that raised homocysteine levels are linked with deficiencies in vitamin B_9 and vitamin B_{12} ($P \leq 0.0001$). A highly significant positive correlation between homocysteine and lipid profile between G1 and G3, and G2 and G3 (P-value≤0.0001). Also, a significant positive correlation exists between homocysteine and triglyceride between G2 and G3 (P-value=0.012). A negative correlation between homocysteine, vitamin B_9, and vitamin B_{12} at G1, G2, and G3 groups (P-value≤0.0001). The study's findings indicated that increased homocysteine levels, which are caused by deficiencies in vitamin B_{12} and vitamin B_9, raise the risk of cardiovascular disease.

***Keywords*-Acute myocardial infarction, Cardiovascular disease, Vitamin B_{12}, Folic acid, Homocysteine**.

I. INTRODUCTION

Acute myocardial infarction, stroke, peripheral artery disease, and other vascular symptoms of cardiovascular disease are the leading causes of morbidity and mortality in the Western world [1]. A myocardial infarction occurs when the blood flow to a portion of the heart is interrupted; this is nearly always caused by the development of an occlusive thrombus at the site of the rupture or erosion of an atheromatous plaque in the coronary artery, which results in the death of heart cells. In 30% of patients, the infarct-related artery remains permanently occluded if treatment is not received [2]. Traditional risk factors for MI include smoking, diabetes mellitus, hypertension, and hypercholesterolemia [3]. High blood cholesterol and hypertension can exacerbate atherosclerosis via several pathways, including oxidative stress, the renin-angiotensin-aldosterone system (RAAS), and compromised endothelial function. A weakened methionine cycle control linked to hypertension also results in an increased homocysteine level [4].

Thiamine (B_1), riboflavin (B_2), niacin (B_3), pantothenic acid (B_5), pyridoxine (B_6), biotin (B_7), folate (B_9), and cobalamin (B_{12}) are the eight water-soluble vitamins that make up the B vitamin group [5]. A vital nutrient found in fruits and vegetables is folate. It is a coenzyme in methionine regeneration and nucleic acid synthesis [6]. Folate family members serve as acceptors or receptors of one-carbon units and operate as coenzymes in pyrimidine and purine synthesis and different methylation processes [7]. Vitamin B_{12}, also referred to as cobalamin, has been referred to as the most aesthetically pleasing cofactor in nature. It is unquestionably the most chemically intricate cofactor of natural origin. It is a cofactor for three reactions: the conversion of homocysteine to methionine, the conversion of 5-methyltetrahydrofolate to tetrahydrofolate, and the conversion of methylmalonic acid to succinyl coenzyme A [8-10]. The development of cardiovascular disease has been linked to an increased amount of homocysteine in the blood, which can result from a deficiency of any of these B vitamins [11].

A sulfur amino acid, homocysteine (Hcy), makes up 70–80% of the total homocysteine in plasma bound to proteins like albumin, with the remainder circulating as free sulfides. [12]. Homocysteine is one of the metabolic intermediates of the essential amino acid methionine. B vitamins such as vitamin B_6, vitamin B_{12}, and folate are necessary for homocysteine metabolism. [13]. In case the oral intake of methionine is low, homocysteine is primarily

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transformed into methionine. This reaction is called remethylation and requires 5-methyltetrahydrofolate (5-MTHF, vitamin B_9) as substrate and vitamin B_{12} as a cofactor for the catalyzing enzyme methionine synthase (MS) [14]. Homocysteine is regenerated to methionine by folate and vitamin B_{12}-mediated reactions in the methionine cycle [15]. A deficiency of folic acid and vitamins slows methionine metabolism and thus increases homocysteine [16]. Increased homocysteine is linked to oxidative stress brought on by the buildup of reactive oxygen species and vascular inflammation. These inflammatory pathways may have synergistic effects, and measurements could provide additional information regarding the risk of atherosclerotic cardiovascular disease [17]. However, the significance of homocysteine in the development of cardiovascular disease is still a topic of discussion, and the results from studies exploring this link have been inconsistent [18].

This study aimed to demonstrate the homocysteine, vitamin B_9, vitamin B_{12}, and lipid profile levels in patients with acute myocardial infarction and early-stage heart disease compared to controls and to assist in the correlation among these parameters in showing their effects on the studied groups. That was done by estimating homocysteine, vitamin B_{12}, and vitamin B_9 by Huma reader HS Elisa, measuring the lipid profile by Semi-Auto Chemistry Analyser BA-88a.

II. PATIENTS AND METHODS

A. *Design Study*

This case-control study was performed at the critical care unit (CCU) in Baquba General Hospital for patients with acute myocardial infarction and early-stage heart disease in Diyala, Iraq.

A total of one hundred twenty participants were selected for this study, aged between 30 to 70 years. Forty patients with acute myocardial infarction were chosen from those attending Baquba General Hospital, and forty patients with early-stage heart disease from November 2024 to February 2025. The diagnosis of acute myocardial infarction was performed based on the recommended criteria by the WHO [19]. A control group of forty healthy participants with no chronic illnesses, no heart failure, diabetes, or any other disease. “Some data, including homocysteine and lipid profile from this sample, were previously used in a different study focusing on cardiac receptors.”

B. *Methods*

To extract serum, five milliliters of venous blood were collected in gel tubes from the control group and patients with acute myocardial infarction and early-stage heart disease. The blood was allowed to clot at room temperature for ten minutes, and the gel tubes were centrifuged at 4000 x g for 10 minutes. The serum was then gathered into two Eppendorf tubes, and the competitive enzyme-linked immunosorbent assay (ELISA) method was used to quantitatively determine homocysteine, vitamin B_9, and vitamin B_{12} by employing a chemiluminescence analyser (Huma reader HS Elisa Microtiter Plate Reader, which is a semi-automatic, microprocessor-controlled photometer). Cho., TG, HDL, and LDL were quantified in this investigation using the Semi-Auto Chemistry Analyser BA-88a [Mindray, China].

C. *Statistical Analysis*

Data analysis was carried out using the available statistical package of IBM SPSS-29 (version 29). The data were analysed using a chi-square test to compare the percentages. One-way ANOVA with post hoc analysis was used to investigate differences between the studied groups (more than two). Pearson Correlation: to examine the degree of relation between variables. The correlation coefficient value (r) is either positive (direct correlation) or negative (inverse correlation). The sensitivity and specificity of the studied parameters were evaluated by a receiver operating characteristic (ROC) curve. The (P-value≤0.05) was considered as significant (S), and the (P-value≤0.01) was considered as highly significant (H.S).

III. RESULTS

Figure 1 shows the demographic characteristics of the randomly selected study population. One hundred twenty participants selected, 31.4% in G1 and 31.4% in G2, compared to 37.1% in G3, belong to the age group (30-44 years), in the age group (45=59 years), 29% in G1 and 31.4% in G2, compared to 39% in G3. Whereas in the age group (60-70), 41.2% in G1 and 38.2% in G2, compared to 20.6% in G3.

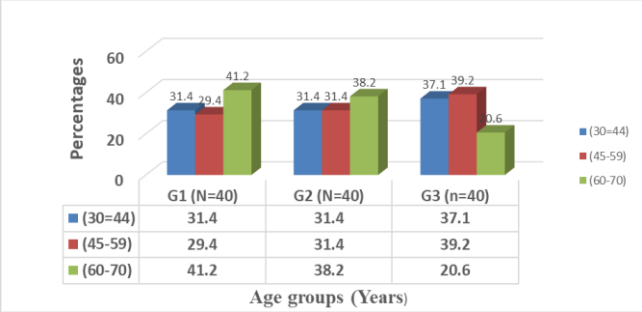

Fig. 1: Demographical properties of age in cases G1: Acute myocardial infarction; G2: Early-stage heart disease; and G3: Control group

There is a highly significant difference in sex between G1 and G2 compared to G3. Males were more than females in the group with acute myocardial infarction, while females were more than males in the group with early-stage heart disease, as shown in Figure 2.

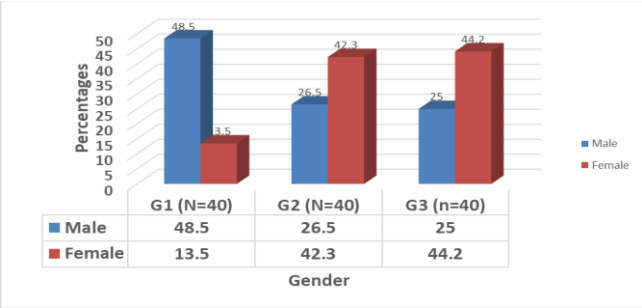

Fig. 2: Demographical properties of gender in cases G1: Acute myocardial infarction; G2: Early-stage heart disease; and G3: Control group

As shown in Table 1, homocysteine was found to be increased in acute myocardial infarction (1882.52±187.27) and early-stage heart disease patients (1653.72±106.83) compared to the controls (344.34±14.71), with a highly significant difference (P ≤0.0001). Vitamin B_9 levels were significantly decreased in acute myocardial infarction and early-stage heart disease patients compared to the controls as follows: G1 (622.71±64.40), G2 (904.54±107.32), G3 (1511.83±132.94) (P ≤0.0001). There was also a significant difference in vitamin B_9 levels between G1 and G2. The levels of vitamin B_{12} were significantly lower in the acute myocardial infarction group (904.63±67.91) and early-stage heart disease patients (1264.73±121.73) in comparison with the controls (2181.11±133.88) (p ≤0.0001).

Table 1: Comparison of the mean levels of Hcy, vitamin B_9 and vitamin B_{12} between G1: acute myocardial infarction, G2: early-stage heart disease and G3: control group

	Groups			P-value
	G1- *Mean ±SD*	G2- *Mean ±SD*	G3- *Mean ±SD*	
Hcy (ng/ml)	[a, b] 1882.52± 187.27	[a] 1653.72± 106.83	344.34± 14.71	≤0.0001
Vitamin B_9 (pg/ml)	[a, b] 622.71± 64.40	[a] 904.54± 107.32	1511.83± 132.94	≤0.0001
Vitamin B_{12} (pg/ml)	[a, b] 904.63± 67.91	[a] 1264.73± 121.73	2181.11± 133.88	≤0.0001

a: significant compared to the control group, b: significant compared to the early-stage heart disease group.

The mean level of serum triglyceride in the acute myocardial infarction group was (209.38± 33.58), and in the early-stage heart disease group was (218.70± 97.17), which was significantly more than the mean levels of triglyceride in the controls (129.09±19.05) (P ≤0.0001). Also, the mean serum total cholesterol level in the acute myocardial infarction group and early-stage heart disease patients was significantly higher than that of the controls (239.79±50.50, 261.18±38.77 versus 143.0±22.40), respectively. The mean serum LDL-cholesterol was (142.92±13.98) in acute myocardial infarction and (208.51±15.46) in early-stage heart disease patients, compared to the control group (86.20±9.2). The mean HDL cholesterol was shown to be considerably lower in the acute myocardial infarction group (32.77±2.23) and early-stage heart disease group (34.03±3.97) compared to the control group (46.35±3.84), as demonstrated in Table 2.

Table 2: Mean levels of lipid profile parameters between G1: acute myocardial infarction: G2: early-stage heart disease and G3: control group

Test	Groups			P-value
	G1- *Mean ±SD*	G2- *Mean ±SD*	G3- *Mean ±SD*	
TG (mg/dl)	[a] 209.38± 33.58	[a] 218.70± 97.17	129.09±19.05	≤0.0001
Cho (mg/dl)	[a,b] 239.79± 50.50	[a] 261.18± 38.77	143.0± 22.40	≤0.0001
LDL (mg/dl)	[a,b] 142.92± 13.98	[a] 208.51± 15.46	86.20±9.2	≤0.0001
HDL (mg/dl)	32.77±2.23	34.03±3.97	46.35±3.84	≤0.0001

a: significant compared to the control group, b: significant compared to the early-stage heart disease group.

Table 3 revealed a strong negative relationship between Hcy and vitamin B_9 (r= -0.823), vitamin B_{12} (r= -0.690), and HDL (r= -0.781), while there was a Strong positive Correlation with Cho. (r=0.636), TG (r =0.703) and LDL (r =0.769).

Table 3: Correlation analysis of Hcy levels with studied parameters between the acute myocardial infarction group (G1) and the control group (G3)

Test	r	P-value	Sig.	Correlation score
Vitamin B_9 (pg/ml)	-0.823**	≤0.0001	H. S	Strong negative
Vitamin B_{12} (pg/ml)	-0.690**	≤0.0001	H. S	Strong negative
TG (mg/dl)	0.703**	≤0.0001	H. S	Strong positive
Cho (mg/dl)	0.636**	≤0.0001	H. S	Strong positive
LDL (mg/dl)	0.769**	≤0.0001	H. S	Strong positive
HDL (mg/dl)	-0.781**	≤0.0001	H. S	Strong negative

** Correlation is significant at the 0.01 level

Table 4 shows a weak negative relationship between Hcy and vitamin B_9 (r = -0.460) and a strong negative relationship with vitamin B_{12} (r= -0.731) and HDL (r= -0.630), while a Strong positive relationship with Cho. (r= 0.722), LDL (r =0.776), and a weak positive relationship with TG (r =0.280).

Table 4: Correlation analysis of Hcy (ng/ml) levels with studied parameters between the early-stage heart disease group (G2) and the control group (G3)

Test	R	P-value	Sig.	Correlation score
Vitamin B_9 (pg/ml)	-0.460	≤0.0001	H. S	Weak negative
Vitamin B_{12} (pg/ml)	-0.731**	≤0.0001	H. S	Strong negative
TG (mg/dl)	0.280	0.012	S	Weak positive
Cho (mg/dl)	0.722**	≤0.0001	H. S	Strong positive
LDL (mg/dl)	0.776**	≤0.0001	H. S	Strong positive
HDL (mg/dl)	-0.630**	≤0.0001	H. S	Strong negative

** Correlation is significant at the 0.01 level

The relationship between Hcy and vitamin B9 in the acute myocardial infarction group is weakly negative (r= -0.366) and moderately negative with vitamin B_{12} (r= -0.522). In early-stage heart disease patients, the relationship between Hcy and vitamin B_9 is weakly positive (r=0.108), and with vitamin B_{12}, it is weakly negative (r=-0.491), as shown in Table 5.

Table 5: Correlation analysis of Hcy (ng/ml) levels with studied parameters between the acute myocardial infarction group (G1) and the early-stage heart disease group (G2)

Test	G1: Acute myocardial infarction		G2: Early-stage heart disease	
	r	P-value	r	P-value
Vitamin B_9 (pg/ml)	-0.366	0.020	0.108	.507
Vitamin B_{12} (pg/ml)	-0.522	0.001	-0.491	0.001

** Correlation is significant at the 0.01 level

The receiver operating characteristic curve (ROC) analysis was done to assess the diagnostic value of Hcy (ng/ml), vitamin B_9 (pg/ml), and vitamin B_{12} (pg/ml) in acute myocardial infarction patients. The results of ROC analysis of Hcy (ng/ml), vitamin B_9 (pg/ml), and Vitamin B_{12} (pg/ml) are shown in Table 6 and Figure 3 an excellent prediction of AUC value result was seen for Hcy (ng/ml), vitamin B_9 (pg/ml), and vitamin B_{12} (pg/ml) with (P=0.001,0.001,0.001) at 0.948,0.035,0.074 respectively. The sensitivity was 92.5%, 97%, and 95%, and the Specificity was 97.5%, 0%, and 0%, respectively, at optimal cutoff values of more than 980, 425, and 793.67, differentiating patients from the control group.

Table 6: ROC analysis of studied parameters between the myocardial infarction group (G1) and the control group (G3)

Test	Area	cutoff	P-value	Sensitivity	Specificity
Hcy(ng/ml)	0.948	980	0.000	92.5	97.5
Vitamin B_9 (pg/ml)	0.035	425	0.000	97	0
Vitamin B_{12} (pg/ml)	0.074	793.67	0.000	95	0

*Significant difference at 0.05 level

The results of ROC analysis of Hcy (ng/ml), vitamin B_9 (pg/ml), and vitamin B_{12} (pg/ml) are shown in Table 7 and Figure 4 an excellent prediction of AUC value result was seen for Hcy (ng/ml), Vitamin B_9 (pg/ml), and vitamin B_{12} (pg/ml) with (P=0.001,0.001,0.001) at 0.936, 0.154, 0.09 respectively. The sensitivity was 95%, 97%, and 92%, and the specificity was 92.5%, 1%, and 1 %, respectively, at optimal cutoff values of more than 846.24, 721.59, and 1138.77, which differentiated early-stage heart disease groups from controls.

Table 7: ROC analysis of studied parameters between the early-stage heart disease group (G2) and the control group (G3)

Test	Area	cutoff	P-value	Sensitivity	Specificity
Hcy (ng/ml)	0.936	846.24	0.000	*95*	*92.5*
Vitamin B_9 (pg/ml)	0.154	721.59	0.000	97	1
Vitamin B_{12} (pg/ml)	0.09	1138.77	0.000	92	1

*Significant difference at 0.05 level

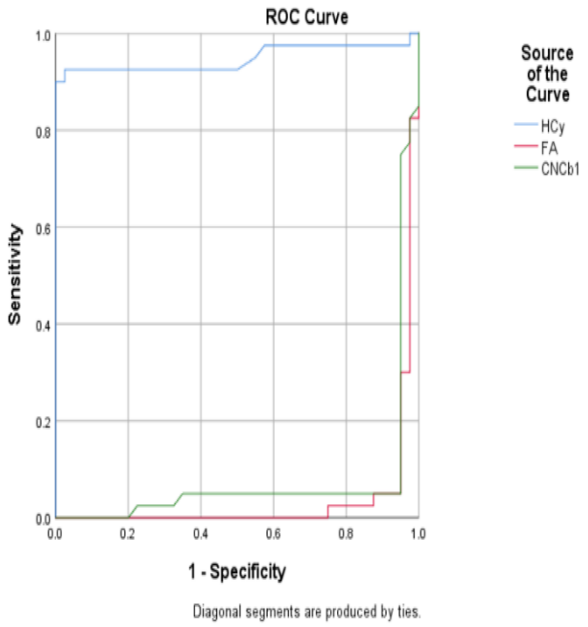

Fig. 3: ROC Curve of homocysteine, vitamin B_9, and vitamin B_{12} between acute myocardial infarction patients and controls

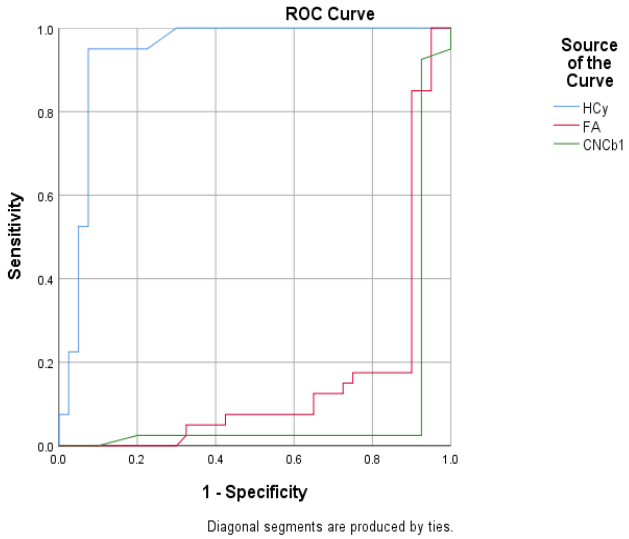

Figure 4: ROC Curve of homocysteine, vitamin B_9, and vitamin B_{12} between early-stage heart disease patients and controls

IV. DISCUSSION

The average age of patients with acute myocardial infarction (AMI) in the present investigation was 53.14 years, which is compatible with a report from Iraq that reported that the mean age was 55.9 years [20]. Our results are seven years less than a report from Al-Wahdah Teaching Hospital, Yemen, which demonstrated the mean age was 60.13 years [21]. However, acute myocardial infarction in the oldest-old is poorly understood [22]. The mean age of patients with early-stage heart disease in group 2 was 52.26 years, which is less than two years than the finding of a Chinese study, which found the mean age was 56·4 years [23].

In this study, males have a higher incidence of acute myocardial infarction than females. This result agrees with Alkhouli *et al.*, who discovered that women have a lower incidence of AMI and a lower likelihood of undergoing invasive treatment than men [24]. Other studies by Sharif *et al.* in Sulaimani City found a higher occurrence of myocardial infarction in male patients than in females [25]. In the group with early-stage heart disease, females were more than males, which agrees with Walli-Attaei *et al.*, who found women have a higher cardiovascular risk than do men, especially at younger ages [26].

Our study showed raised homocysteine levels in acute myocardial infarction patients compared to controls. This agrees with Habib *et al.*, in the Saudi Arabia found that homocysteine is significantly correlated with atherosclerotic cardiovascular disease in overweight and youthful patients [27].

In contrast, the homocysteine level in a group with early-stage heart disease is also higher than in a control group. This result agrees with Shih *et al.*, whose study showed that elevated homocysteine levels are linked with high cardiovascular disease risk [28]. Other studies by Hassan Muslim *et al.* found that hyperhomocysteinemia raises the risk of cardiovascular thrombosis in younger patients with coronary artery disease [29].

The results of this study demonstrated that the homocysteine level in patients with hyperlipidemia is higher than the level in the control group. This agrees with the study results by Ren *et al.*, who found that serum homocysteine correlates with elevated lipid levels [30]. Other studies by Wu *et al.* showed that hyperhomocysteinemia was related to the atherogenic lipid profile in patients with coronary artery disease [31]. Hyperhomocysteinemia increased the biosynthesis and secretion of cholesterol and triglycerides and decreased HDL-C levels [32].

The results of this study showed high levels of triglyceride, total cholesterol, LDL, and lower levels of HDL in patients with acute myocardial infarction compared to the control group. These results agree with those of Dr. Venkateshwarlu, M. and Dr.Chelmakuri Gayathri, who found that acute myocardial infarction patients displayed elevated levels of total cholesterol, LDL, and triglyceride, along with lower HDL levels, compared to the control group [33].

This study demonstrates the negative relationship between homocysteine, vitamin B_9, and vitamin B_{12}. This result agrees with Sowndarya *et al.*, who showed a substantial negative correlation between homocysteine levels and vitamin B12 and vitamin B9 [34]. It also agrees with Marwa Hameed Hussien and Mohammed A. Auda, who found that low folic acid contributed to increased homocysteine and a negative relationship between it and homocysteine [35].

V. CONCLUSIONS

The relationship between homocysteine, B vitamins, and fats is crucial for preserving cardiac health. The accumulation of lipids in the heart's blood vessels and an elevated risk of atherosclerosis, the primary cause of cardiovascular disease, are the consequences of a deficiency in vitamin B_9 and vitamin B_{12}, which results in an elevated level of homocysteine in the blood. It is imperative to monitor and follow up on the levels of these supplements, as they contribute to the rise in homocysteine for decreased risk of cardiovascular disease.

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CONFLICT OF INTEREST

Authors declare that they have no conflict of interest.

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