Journal of Cardiovascular Disease Research
ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 01, 2023

The Role of homocysteine and MCP-1 Levels in Patients with Angina Pectoris or Congestive Heart Failure

Zainab Samir Yahya Hammo[1], Zaid Mohammed Mubarak Almahdawi[2], Sahlah Khorsheed Abbas[3] , Suadat Mustafa Mohammed Al-Hermizy[4] and Noor Thair Tahir[5]

Department of Physiology, College of Medicine, University of Tikrit, Iraq zainabsamir1986@gmail.com [1]

Al-Imam University College, Tikrit, Iraq zaid.almahdawi@yahoo.com [2]

College of Science, University of Kirkuk, Iraq Sahlalmmuno@uokirkuk.edu.iq [3]

Department of Biology, College of Science, University of Tikrit, Iraq Suadmustafa300@gmail.com [4]

National Diabetes center, Al- Mustansiriyah University, Baghdad, Iraq dr.noorthair.ndc@uomustansiriyah.edu.iq [5]

Abstract

Background: Homocysteine is an amino acid produced when proteins are broken down. A high homocysteine level, also called hyperhomocysteinemia, can contribute to arterial damage and blood clots in blood vessels.

Objectives: This study aims first to determine the levels of MCP-1 and HCY in patients with angina pectoris and congestive heart failure, and then to determine their role in both diseases.

Methods: This study was carried out at Salah Al-Deen Hospital in Tikrit from the 1st of January 2022 to 30th of March 2022. The study included 70 males patients, 35 of them have congestive heart failure (G1) and 35 have angina pectoris (G2), range of the ages are between (40-70) years old. After checking their conditions throughout medical and clinical tests by specialist physician in this aspect. As well as choosing random group included 20 samples of healthy males of ages between (40-70) years old as a control group (C).

Results: Serum levels of HCYand MCP-1 in patients groups (G1,G2) were significantly elevated, compared to the healthy subjects (C), (p P<0.01). On the other hand there was statistically significant difference between congestive heart failure and angina pectoris patients. Additionally, this study further confirmed positive correlations between plasma HCY levels and MCP-1, Total Protein and Globulin in patients with CHF and Angina Pectoris. On the other hand, they negatively correlated with albumin in the same groups.

Conclusion: In conclusion, Homocysteine, which is a natural amino acid found in cells and plasma, plays a major role in destroying the arteries of the body more than smoking, obesity or cholesterol itself does. Perhaps it can be said through this study that there is a significant effect of homocysteine among

several parameters, which may have an impact on the development of disease severity and its development, especially its relationship MCP-1. MCP-1 has a role in the development of CVD through important diseases, namely obesity, arteriosclerosis and diabetes, which are considered among the main causes of the emergence and development of heart diseases in general and congestive heart failure and angina pectoris in particular.

Abbreviation: CHF: Congestive Heart Failure; HCY: Homocysteine; MCP-1: monocyte chemotactic protein-1; CVD: Cardiovascular Diseases

Keywords: *Congestive Heart Failure, Angina Pectoris, HCY, MCP-1.*

INTRODUCTION

Homocysteine is remethylated to methionine or catabolized to cystathionine. The major remethylation pathway requires folate and cobalamin (vitamin B12) and involves the action of methylenetetrahydrofolate reductase (MTHFR); a minor remethylation pathway is mediated by betaine–homocysteine methyltransferase. Alternatively, homocysteine is converted to cystathionine in a trans-sulfuration pathway catalyzed by cystathionine β-synthase (CBS), with pyridoxine used as a cofactor. Elevated homocysteine is a known risk factor for cardiovascular disease as well as thrombosis (Fujiwara, *et al*., 2018). It has also been shown to be associated with microalbuminuria which is a strong indicator of the risk of future cardiovascular disease and renal dysfunction. Homocysteine degrades and inhibits the formation of the three main structural components of arteries: collagen, elastin and proteoglycans. In proteins, homocysteine permanently degrades cysteine disulfide bridges and lysine amino acid residues, affecting structure and function(Guo, *et al*., 2022). Homocysteine has been under a lot of speculation since its discovery in 1932. Its chemical properties showed a similarity to cysteine, hence the name homocysteine. The heating of the amino acid methionine with sulphuric acid led to this amino acid of interest (Kim, *et al.*, 2018). The importance of this discovery cannot be emphasized on without alluding to the 1955 Nobel Prize in Chemistry, awarded to Vincent du Vigneaud For his work on biochemically important sulphur compounds, especially for the first synthesis of a polypeptide hormone. Recent years have shown a dramatic increase in research towards the better understanding of the notoriety of this amino acid of interest (Djurovic, *et al*., 2021).

Monocyte Chemotactic Protein-1(MCP-1)

Chemokines (chemtactic cytokines) are small heparin-binding proteins that constitute a large family of peptides (60–100 amino acids) structurally related to cytokines, whose main function is to regulate cell trafficking. Chemokines were first identified in 1977 with the purification of the secreted platelet factor 4. Since then, studies have identified more than 50 human chemokines and 20 chemokine receptors. Chemokines can be classified into four subfamilies on the basis of the number and location of the cysteine residues at the N-terminus of the molecule and are named CXC, CC, CX3C, and C, in agreement with the systematic nomenclature (Weber, *et al*., 2010). The genes for CXC chemokines are tightly and clustered mainly on chromosome 4, whereas the members of CC chemokines are encoded by

genes that are located mainly on chromosome 17. Chemokines are secreted in response to signals such as proinflammatory cytokines where they play an important role in selectively recruiting monocytes, neutrophils, and lymphocytes. Once induced, the directed migration of cells expressing the appropriate chemokine receptors occurs along a chemical ligand gradient known as the chemokine gradient (Chen, *et al*., 2019). This allows cells to move toward high local concentrations of chemokines. The structure of chemokines comprises three distinct domains:

- a highly flexible N-terminal domain, which is constrained by disulfide bonding between the N-terminal cysteine(s)
- a long loop that leads into three antiparallel β-pleated sheets
- an α-helix that overlies the sheets (Figure 1) (Blanco-Colio, *et al*., 2022).

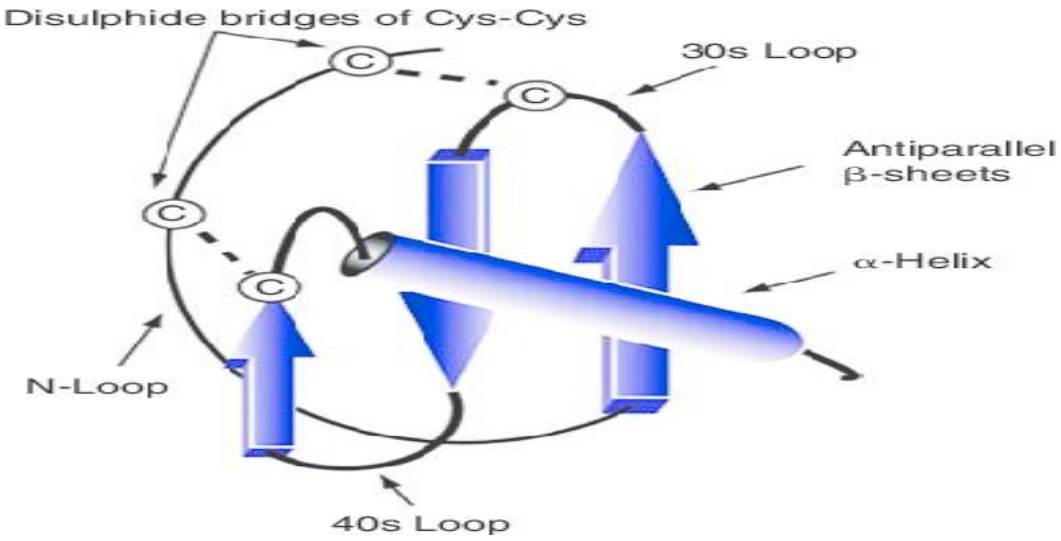

Figure (1): Schematic representation of the three-dimensional structure of chemokines. Three-dimensional representation of a chemokine, where α and β sheet, as well as the cysteine residues and the 30s and 40s loops, are shown. Note that all chemokines share a typical Greek key structure that is stabilized by disulfi de bonds between conserved cysteine residues. The term Greek key refers to a kind of secondary structure or motif of a protein sequence

CCL2 is produced by many cell types, including endothelial, fibroblasts, epithelial, smooth muscle, mesangial, astrocytic, monocytic, and microglial cells. These cells are important for antiviral immune responses in the peripheral circulation and in tissues. However, monocyte/macrophages are found to be the major source of CCL2. CCL2 regulates the migration and infiltration of monocytes, memory T lymphocytes, and natural killer (NK) cells. Note that CCL2 is among the most studied member of the chemokine family, and has been shown to be a potential intervention point for the treatment of various diseases, including multiple sclerosis, rheumatoid arthritis, atherosclerosis and insulin resistant diabetes (Chen, *et al*., 2012; Alkanaani, *et al*.,2020). This study aims first to determine the levels of MCP-1 and

HCY in patients with angina pectoris and congestive heart failure, and then to determine their roles in both diseases.

MATERIALS AND METHODS

This study was carried out at Salah Al-Deen Hospital in Tikrit from the 1st of January 2022 to 30th of March 2022. The study included 70 males patients, 35 of them have congestive heart failure (G1) and 35 have angina pectoris (G2), range of the ages are between (40-70) years old. After checking their conditions throughout medical and clinical tests by specialist physician in this aspect. As well as choosing random group included 20 samples of healthy males of ages between (40-70) years old as a control group (C) (Table 1).

The present study included 70 blood samples were collected from males who have angina pectoris and congestive heart failure and from healthy males their ages between (40-70) years old. Venous samples were taken early in the morning for the patient and control groups, after at least 12-hours of fasting and a 20- minute rest. The samples of blood were drawn from the median cubital vein or from another vein if this was not accessible. After cleaning the venipuncture site with iodine using concentric circles, the iodine

remained in contact with the skin until dried to ensure disinfection. After that 5 ml of blood was taken and put in the gel tube, gel tube has been put in the cool box (contained ice bag) till transport to the emergency unit laboratory and separated by centrifuging for 10 minutes at 6000 rpm. After separation of whole blood the serum was extracted by using micropipette, after that 2 ml of blood serum was put in three eppendorf tubes to make hormonal, immune, and biochemical tests. And then stored in a deep freezer (-20°C). The information of each participant was recorded through a questionnaire sheet include age, sex, weights, patient's residency and other information. Detection of HCY, MCP-1, Total Protein, Albumin and Globulin levels in the serum were determined by an enzyme linked immunosorbent assay (ELISA) kits.

Table (1):- Demographic Distribution of Study Population

Groups	No. of Individuals	Age (years)
G1	35	
G2	35	(40-70) years old
C	20	

Statistical analysis

The statistical analysis was carried out by using statistical program (Minitab) and comparison between groups which were made by using one-way analysis of variance ANOVA and tried out the arithmetic means for parameters by using test of Duncan's multiple range test to delimitating significantly difference especially between groups. Pearson correlation coefficient (R) between nesfatin and other parameters was reported by using regression plots. The level of statistical significance was taken at ($P \leq 0.01$) and ($P \leq 0.05$) (Popović, 2021).

RESULTS and DISCUSSION

The results of this study revealed that The mean ± SD of homocysteine levels for congestive heart failure, angina pectoris patients and control groups respectively were (24.59 ± 5.59) µmol/L, (20.59 ± 4.550) µmol/L and (10.10 ± 2.002) µmol/L, as shown in table (2) and figure (2). In the present study, there was high significant difference ($P \leq 0.01$) between the three groups (for Homocysteine hormone) in the view of mean of parity ($p=0.00001$). Homocysteine hormone increased in CHF and angina pectoris patients groups more than control group. These results agreed with Guo *et al*. (2022); Khaleefah *et al.* (2021); Jin *et al.* (2021) and Bajic *et al.* (2022), but no researches disagreed with these findings.

Chemokines are potent proinflammatory and immune modulators. Increased expression of chemokines, eg, monocyte chemoattractant protein-1 (MCP-1), has recently been described in clinical and experimental heart failure and angina pectoris. The mean ± SD of MCP-1 levels for congestive heart failure, angina pectoris patients and control groups respectively were (281.64 ± 24.04) pg/ml, (206.00 ± 28.19) pg/ml and (128.36 ± 21.81) pg/ml, as shown in table (2) and figure (3). In this study, there was high significant difference ($P \leq 0.01$) between the three groups (for MCP-1) in the view of mean of parity ($p= 0.0009$). MCP-1 levels were significantly higher in patients groups than control group, on the other hand there was statistically significant difference between CHF and angina pectoris patients, MCP-1 in CHF patients was higher than angina pectoris patients. These current results are compatible with results for Blanco-Colio *et al.* (2022); Makarewicz-Wujec, *et al.* (2022) and Georgakis, *et al*. (2022). However, the current results are incompatible with results for Mohamed *et al.* (2020) and Zaman *et al.* (2021), they found MCP-1 level was significant higher in angina pectoris than CHF and control groups. This difference in results may be due to several reasons, including the amount of thrombus formed, the degree of thrombus, the type of atheroma formed, is it stable or unstable, as well as the amount of macrophages infiltrating the artery, and many factors that will be clarified by this study through researchess that have already been conducted before.

Additionally, the mean ± SD of protein profile levels for congestive heart failure, angina pectoris patients and control groups respectively were shown in table (3) and figures (4,5,6). Total protein and globulin levels were significantly higher in patients groups than control group (P=0.00001, 0.00006 respectively), while albumin levels on the contrary, were lower in patients groups than control group (P=0.00002). These current results are compatible with results for Lind, *et al.* (2022); Stenemo, *et al.* (2020) and El Iskandarani, *et al.* (2021). However, the current results are incompatible with results for Immler, *et al.* (2022); Mattisson, *et al. (*2019) and Su, *et al.* (2019) . The first and second one found that albumin level was higher in patients compared with control groups, whereas total protein levels were normal in patients. The third one found that albumin levels remained unchanged.

Table (2) Arithmetic average for Parameters Concentrations in the studied groups

No. / Group	HCY (µmol/L)	MCP-1 (pg/ml)
	Mean ± S.D	Mean ± S.D
G1 n=35	24.59 ± 5. 59 a	281.64 ± 24.04 a
G2 n=35	20.59 ± 4.550 b	206.00 ± 28.19 b
C n=20	10.10 ± 2.002 c	128.36 ± 21.81 c
P- value	P= 0.00001**	P = 0.0009**

Table (3) Arithmetic average for Parameters Concentrations in the studied groups

No. / Group	Total protein (g/dl)	Albumin (g/dl)	Globulin (g/ dl)
	Mean ± S.D	Mean ± S.D	Mean ± S.D
G1 n=35	9.90 ± 1.256 a	2.19 ± 0.5208 b	7.73 ±1.340 a
G2 n=35	9.69 ± 1.087 a	2.53 ± 0.4077 b	7.18 ± 1.133 a
C n=20	6.53 ± 0.479 b	3.82 ± 0.549 a	2.71 ± 0.666 b
P- value	P =0.00001**	P =0.00002**	P = 0.00006**

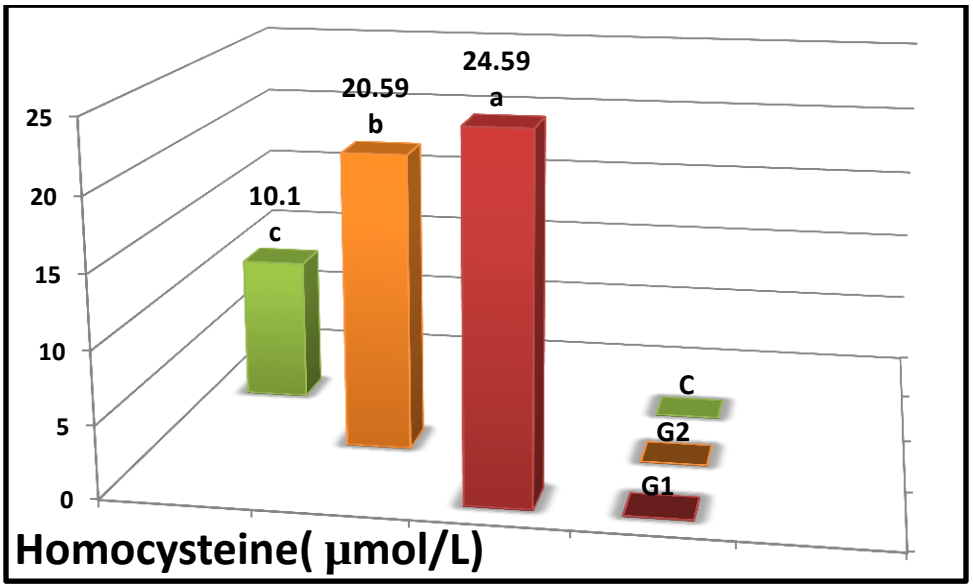

Figure (2): Levels of homocysteine µmol/L in patients and control groups.

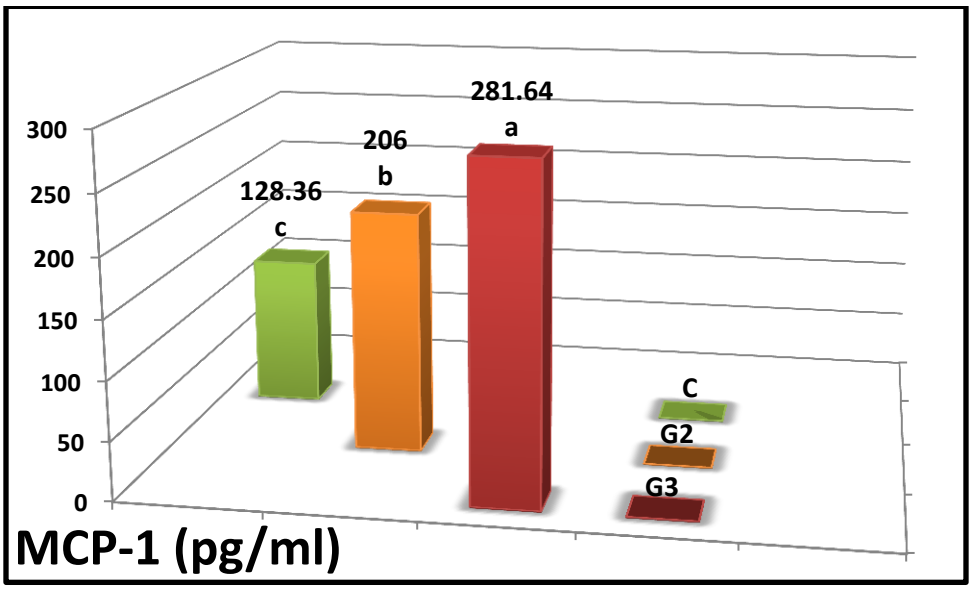

Figure (3): Levels of MCP-1 pg/ml in patients and control groups

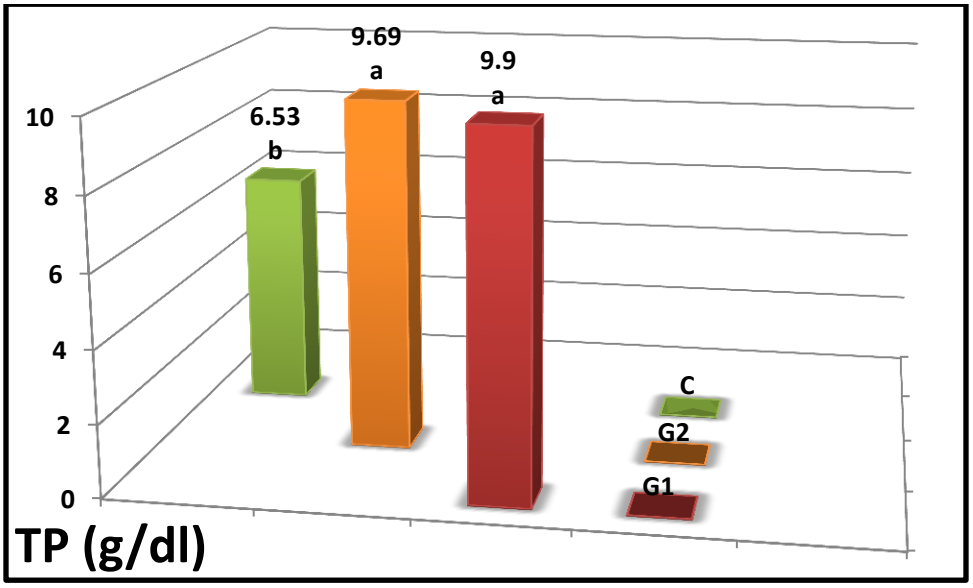

Figure (4): Levels of Total protein (g/dl) in patients and control groups.

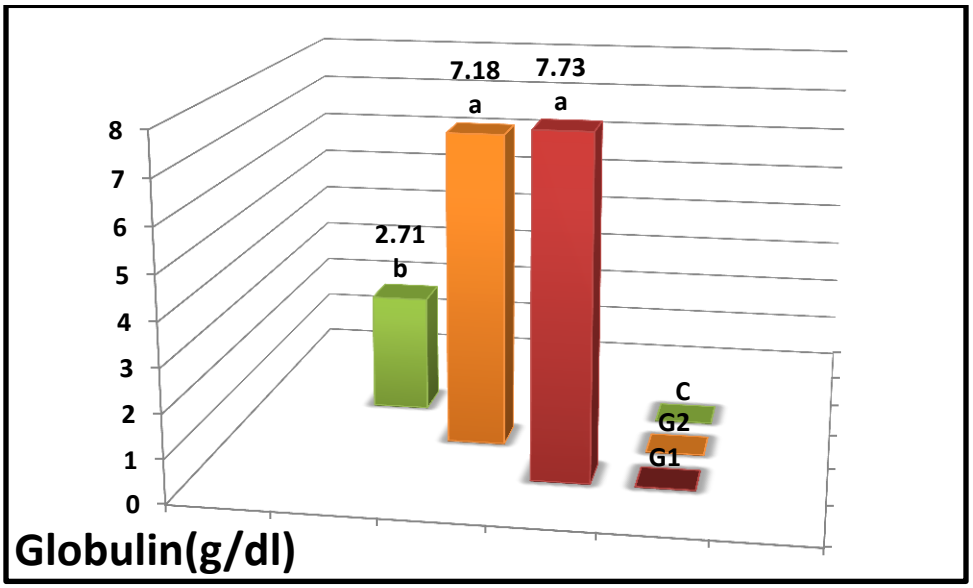

Figure (5): Levels of Globulin (g/dl) in patients and control groups

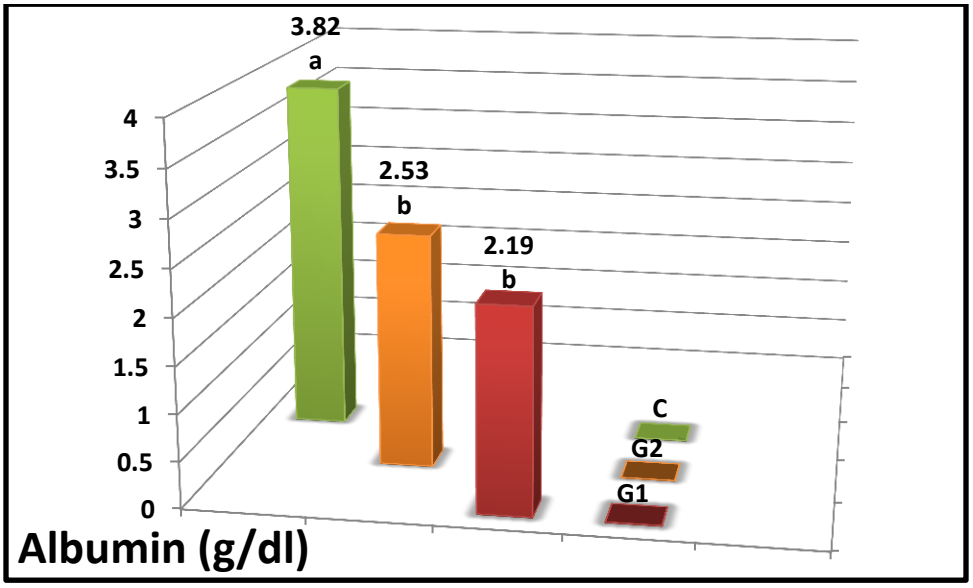

Figure (6): Levels of Albumin (g/dl) in patients and control groups.

Note: The similar letters mean that there are no significant differences between vertical groups and the different letters mean that there are significant differences between them at a potential level P ≤ 0.01(**).G1, Congestive Heart Failure patients; G2, Angina Pectoris patients; C, Healthy Individuals (Control).

The results of Pearson's correlation demonstrated in tables (4,5) and Figures (7,8) observe that: There is positive correlations between plasma HCY levels and MCP-1, Total Protein and Globulin in patients with CHF and Angina Pectoris. On the other hand, HCY negatively correlated with albumin in the same groups.

Table 4: Correlation coefficient (R) between HCY with parameters in Congestive Heart Failure patients

parameters	Statistical variables	MCP-1	Total protein	Albumin	Globulin
HCY	R	0.355	0.484	-0.364	0.312
	P	0.039*	0.008**	0.051*	0.065*
MCP-1	R		0.364	-0.156	0.443
	P		0.051*	0.551ns	0.005**

Table 5: Correlation coefficient (R) between HCY with parameters in Angina Pectoris patients

parameters	Statistical variables	MCP-1	Total protein	Albumin	Globulin
HCY	R	0.374	0.328	-0.407	0.372

	P	0.046	0.058*	0.009**	0.030*
MCP-1	R		0.335	-0.354	0.474
	P		0.046*	0.086*	0.005*

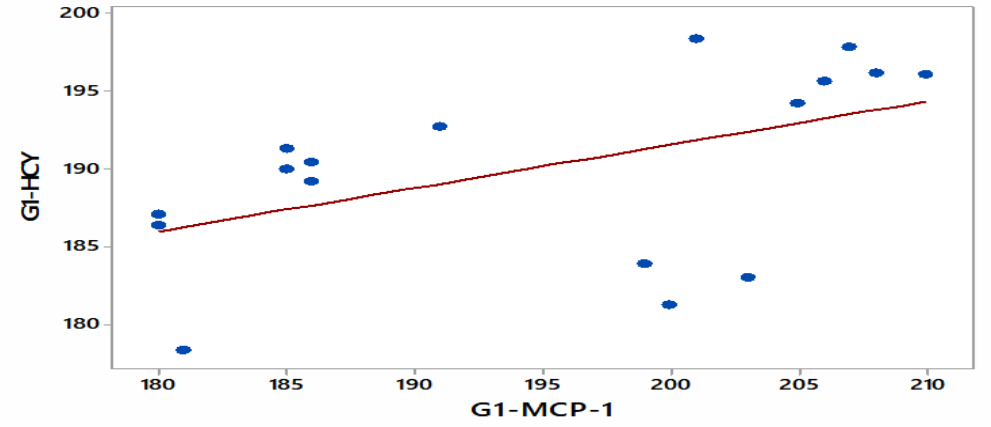

Figure (7) Correlation between HCY with MCP-1in congestive heart failure patients

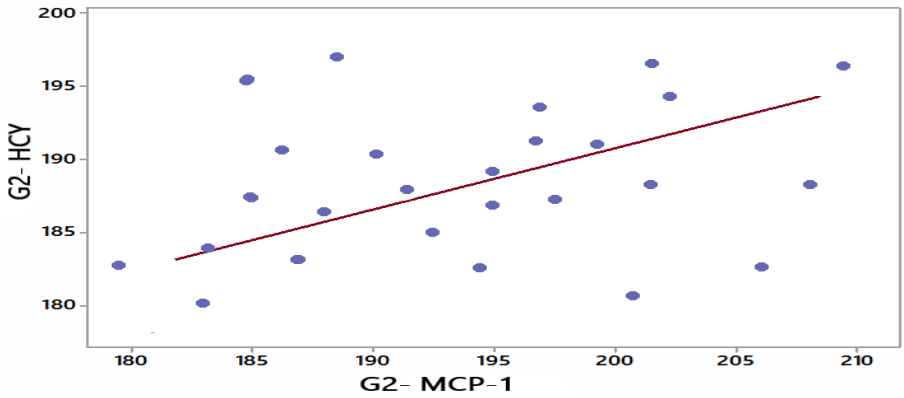

Figure (8) Correlation between HCY with MCP-1in angina pectoris patients

Elizabeth and her assistants estimated that an elevated plasma level of homocysteine (HCY) is associated with increased risk of thrombotic and atherosclerotic vascular disease. Several studies and recent patents have demonstrated that hyperhomocysteinemia is an indipendent risk factor for vascular disease (Yang, *et al.*, 2020). An elevated homocysteine level has been also reported to be a risk factor for the development of congestive heart failure (CHF) in individuals free of myocardial infarction. Animal studies showed that experimental HHCY induces systolic and diastolic dysfunction, as well as an increased BNP expression. Moreover, hyperhomocysteinemic animals exhibit an adverse cardiac remodeling characterized by accumulation of interstitial and perivascular collagen. The

mechanisms leading from an elevated HCY level to reduced pump function and adverse cardiac remodeling are a matter of speculation (Elizabeth, *et al.*, 2016).

Recently, plasma homocysteine has been suggested to be increased in heart failure patients potentially representing another newly recognized risk marker or risk factor. The study results are in agreement with the hypothesis that high plasma homocysteine concentrations are a significant risk factor for heart failure (Chrysant, *et al.*, 2019). Elevated homocysteine levels may promote heart failure through several mechanisms. First, elevated homocysteine concentration is a risk factor for atherosclerosis of coronary vessels. Furthermore, homocysteine can cause ischemia in myocardial tissue by encouraging the endothelial dysfunction of coronary vessels. Second, elevated homocysteine concentration in patients with acute coronary syndrome is associated with larger myocardial injury as evidenced by elevated troponin concentration. Third, the homocysteine role as a source of oxidative stress, a factor recognized to endorse myocardial dysfunction. Fourth, hyperhomocysteinemic rats have amplified cardiac fibrosis and increased activate matrix metalloproteinases, which sequentially encourage remodeling of left ventricle, a recognized originator of congestive heart failure (Feng, *et al.*, 2018; Piek, *et al.*, 2019; Pang, *et al.*, 2018).

While that Bajic his colleagues estimated that homocysteine has been found to be a risk factor or a marker for cardiovascular diseases, including myocardial infarction (MI), angina pectoris and heart failure (HF). There are indications that vitamin B6 plays a significant role in the process of transsulfuration in homocysteine metabolism, specifically, in a part of the reaction in which homocysteine transfers a sulfhydryl group to serine to form α-ketobutyrate and cysteine. Therefore, an elevated homocysteine concentration (hyperhomocysteinemia) could be a consequence of vitamin B6 and/or folate deficiency (Bajic, *et al.*, 2022). Hyperhomocysteinemia in turn could damage the endothelium and the blood vessel wall and induce worsening of atherosclerotic process, having a negative impact on the mechanisms underlying angina pectoris and HF, such as oxidative stress, inflammation, and altered function of gasotransmitters (Jayedi and Zargar, 2019).

Extensive experimental studies, both in vivo and in vitro, have produced conclusive evidence that high homocysteine levels significantly impaired endothelial-dependent vasodilation and resulted in a concurrent attenuated NO bioavailability in response to dilatory stimulus such as acetylcholine, suggesting that homocysteine-induced endothelial dysfunction at least partly stems from the loss of endothelium-dependent relaxing factor (Paganelli, *et al.*, 2021). Also, the observed atherosclerotic changes in hyperhomocysteinemic patients were found related to blood platelet and coagulation activation, and impaired fibrinolysis and chronic inflammation (Sreckovic, *et al.*, 2019).

Examination of the effect of homocysteine on CRP expression and investigation on the related mechanism in vascular smooth muscle cells (VSMCs) revealed that homocysteine significantly induced mRNA and protein expressions of CRP in VSMCs both in vitro and in vivo (Uzelac, *et al.*, 2021).

MCP-1, a member of the C-C chemokine family, is synthetized by endothelial cells, smooth muscle cells and monocytes and macrophages within atherosclerotic plaques (Chen, *et al.*, 2020). What should be noted that IL-6, TNF-a, ET-1, MCP-1 and apelin, they are also considered a cardiokine (Doroudgar *et al.*, 2011). It is known that MCP-1, through its receptor C-C chemokine receptor type 2 (CCR-2) on monocytes, acts as a chemotactic factor to recruit monocytes into the vascular wall. Both CCL2 and its receptor CCR2 have been demonstrated to be induced and involved in various diseases (Moskalik, *et al.*, 2022). The role of MCP-1 in atherosclerotic plaque development and progression has been extensively analyzed. Several lines of evidence indicate that this chemotactic protein is one of the key factors initiating the inflammatory process of atherogenesis (De Lemos, *et al.*, 2017). The expression and release of MCP-1 from the endothelium is induced by multiple chemical stimuli; lipopolysaccarides, cytokines, oxidised low density lipoprotein (LDL), homocysteine, angiotensin II, shear stress and other mediators of atherosclerosis or by interaction between activated neutrophils, platelets, and endothelial cells (Aday and Ridker, 2020). Finally, this chemokine may also activate or increase the expression of adhesion molecules to facilitate monocyte adhesion. The role of MCP-1 in atherosclerotic plaque development and progression has been extensively analyzed (Namiki, *et al.*, 2022).

Many of the major diseases, including cardiovascular disease, are widely recognized as inflammatory diseases. MCP-1 plays a critical role in the development of cardiovascular diseases. MCP-1, by its chemotactic activity, causes diapedesis of monocytes from the lumen to the subendothelial space where they become foam cells, initiating fatty streak formation that leads to atherosclerotic plaque formation (França, *et al.*, 2017). Inflammatory macrophages probably play a role in plaque rupture and the resulting ischaemic episode as well as restenosis after angioplasty (Weber, *et al.*, 2010). There is strong evidence that MCP-1 plays a major role in myocarditis, ischaemia/reperfusion injury in the heart and in transplant rejection. MCP-1 also plays a role in cardiac repair and manifests protective effects under certain conditions. Such protective effects may be due to the induction of protective ER (endoplasmic reticulum) stress chaperones by MCP-1. Under sustained ER stress caused by chronic exposure to MCP-1, the protection would break down resulting in the development of heart failure (Gilbert, *et al.*, 2011). MCP-1 is also involved in ischaemic angiogenesis. The recent advances in the understanding of the molecular mechanisms that might be involved in the roles that MCP-1 plays in cardiovascular disease are reviewed. The gene expression changes induced by the signaling events triggered by MCP-1 binding to its receptor include the induction of a novel zinc-finger protein called MCPIP (MCP-1-induced

protein), which plays critical roles in the development of the pathophysiology caused by MCP-1 production (Gruzdeva, *et al.*, 2017).

Ikeda *et al.* after doing a lot of research, they found enhanced MCP-1 expression has been detected in macrophages, endothelial cells, and vascular smooth muscle cells in the atheromatous plaque. Activation of macrophages by MCP-1 also appears to be involved in the vulnerability of the plaque. Indeed, circulating MCP-1 levels are elevated in patients with acute myocardial infarction and in those with unstable angina, but not in patients with stable angina. Production of MCP-1 and macrophage accumulation are also observed after coronary angioplasty or grafting, indicating that MCP-1 expression may be related not only to instability of atheromatous plaques, but also to the formation of restenotic lesions. The development of therapeutic drugs for atherosclerosis targeted specially against MCP-1 may be useful in the prevention of plaque formation and future myocardial infarction (Ikeda, *et al.*, 2020). At a population level, MCP-1 plasma concentrations are positively correlated with different cardiovascular risk factors (Georgakis *et al.*, 2019). Makarewicz-Wujec and his assistants showed that the achieved decrease in the MCP-1 level was probably related to a change in lifestyle, especially the introduction of an intensive dietary intervention. Statins have been shown to reduce the MCP-1 concentration, but a higher decrease in the dietary approaches to stop hypertension (DASH) group with a comparable percentage of statin therapy use (80% patients in the study group and 84% patients in the control group) indicates an influence of nonpharmacological factors (Makarewicz-Wujec, *et al.*, 2022).

The analysis of correlations between dietary components and MCP-1 level (inverse correlation with the vegetable intake, inverse final MCP-1 level correlation with folic acid intake and strong inverse correlations between changes in MCP 1 concentration and changes in fibre and vitamin C intake in both study groups) clearly indicates that the intake of plant-derived products seems to be the most significant factor. The Mediterranean diet, which is rich in fruits, vegetables, whole grain products, nuts and fish, has already shown to reduce the MCP-1 concentration (Henzel, *et al.*, 2021; Liu, *et al.*, 2019). High adherence to the Mediterranean diet in these studies was related to a decrease in the number of inflammatory markers, including MCP-1. Conversely, a study conducted among obese women showed that a diet showing low dietary inflammatory index is related to low concentrations of MCP-1 (Isaksen, *et al.*, 2020). There is increasing evidence that short-term expression of pro-inflammatory cytokines can be beneficial to the heart (Wilson, *et al.*, 2014). It is well known that obesity-induced diabetes is a major risk factor into the development of cardiovascular disease. In recent years, it has become increasingly clear that obesity involves a low-grade systemic inflammatory condition (Soufer, *et al.*, 2014). Visceral-adipose-related inflammation was shown to accelerate atherosclerosis in mice. Both adipocytes and macrophages are sources of cytokine production, and pro-inflammatory cytokines promote cellular insulin resistance in fat, muscle and liver (Dragomir and Simionescu, 2016). High levels of MCP-1 production are associated with obesity in animals

and humans. Thus the MCP-1/CCR2 system plays a critical role in obesity-induced diabetes in mice. The role of MCP-1 in macrophage infiltration into adipose tissue has been questioned based on results obtained with MCP-1-deficient mice (Tamura, *et al.*, 2008). Recent studies in hypercholesterolemic mice lacking apo E or the low-density lipoprotein receptor have suggested a role for MCP-1 in monocyte recruitment to early atherosclerotic lesions (Ridker, *et al.*, 2020). Platelets can contribute to enhanced MCP-1 levels in CHF. MCP-1 is markedly elevated in serum of CHF patients showing a direct correlation with the severity of symptoms and the degree of left ventricular dysfunction. MCP-1-mediated infiltration of monocytic cells and the biologically active molecules released from dying monocytes are associated with deleterious effects on LV function and the progression of heart failure (Stumpf, *et al.*, 2022). The inflammatory cytokines interferon ã and MCP-1 are increased in patients with unstable angina, particularly in those with raised concentrations of troponin T, suggesting that they are probably related to myocardial cell damage or to plaque rupture and thrombus formation (Chen, *et al.*, 2016). Connie *et al.* demonstrated an increased expression of MCP-1 in the liver and in the circulation during hyperhomocysteinemia. The in vivo and in vitro results suggest that activator protein (AP-1) activation is responsible for HCY induced MCP-1 production in hepatocytes (Connie *et al.*, 2017).

In conclusion, Homocysteine, which is a natural amino acid found in cells and plasma, plays a major role in destroying the arteries of the body more than smoking, obesity or cholesterol itself does. Perhaps it can be said through this study that there is a significant effect of homocysteine among several parameters, which may have an impact on the development of disease severity and its development, especially its relationship MCP-1. Finally, The speculation of this peculiar correlation continues to contribute to the perplexity of the scientific society. Though most research work suggests a relationship, yet there seems to be other evidence that still prevents its inclusion as a biomarker. With every ten steps forward, we might have to face a step or two backward, but this should only further increase the enthusiasm of research in this field. This field definitely needs more research input until a definitive proof is available to cast off any shadow of doubt regarding the correlation between homocysteine and cardiovascular disease. And by linking this study and other studies that preceded it, which were referred to previously, it was found that MCP-1 has a role in the development of CVD through important diseases, namely obesity, arteriosclerosis and diabetes, which are considered among the main causes of the emergence and development of heart diseases in general and congestive heart failure and angina pectoris in particular. These properties generated significant interest in the potential significance of MCP-1 as a biomarker in HF. Emerging evidence suggests that MCP-1 plasma levels have prognostic value in the acute and chronic phase following MI, providing information independent of standard clinical variables. High plasma MCP-1 levels may reflect a higher burden of atherosclerotic disease, may exert prothrombotic effects resulting in recurrent

coronary events, or may identify patients who mount a more intense cardiac inflammatory reaction following a coronary event, resulting in enhanced adverse remodeling. Beyond its prognostic significance, the MCP-1 axis may be an attractive target for therapy in patients with HF. Finally, further studies are required to test whether MCP-1 blocking or sophisticated anti-platelet strategies may represent new therapeutic options in CHF.

REFERENCES

Aday, A.W. & Ridker, P.M. 2020. Targeting residual inflammatory risk: a shifting paradigm for atherosclerotic disease. *Front Cardiovasc Med*, **6**:16-21.

Akirov, A., Masri-Iraqi, H., Atamna, A., Shimon, I. 2017. Low Albumin Levels Are Associated with Mortality Risk in Hospitalized Patients. *Am J Med*, **130**:1465.e11-1465.e19.

Alkanaani, M. I., Rajab, E. R., Abdulwahed, A. M. H., Dabos, T., Alshammiri, B., Abdullah, S. N., & AL-Samarraie, M. Q. (2020). Visfatin hormone level and lipid profile in some hyperlipidemia patients in samarra city. *Biochem. Cell. Arch*, 20(1), 1191-1193.

Bajic, Z., Sobot, T., Skrbic, R., Stojiljkovic, M.P., Ponorac, N., Matavulj, A., Djuric, D.M. 2022. Homocysteine, Vitamins B6 and Folic Acid in Experimental Models of Myocardial Infarction and Heart Failure—How Strong Is That Link? .*Biomolecules*, **12(536)**:1-27.

Blanco-Colio, L.M., Méndez-Barbero, N., Pello Lázaro, A.M., Aceña, Á., Tarín, N., Cristóbal, C., Martínez-Milla, J., González-Lorenzo, Ó., MartínVentura, J.L., Huelmos, A. *et al.* 2022. MCP-1 Predicts Recurrent Cardiovascular Events in Patients with Persistent Inflammation. *J. Clin. Med*, **10**:11-37.

Chen, B., Luo, L., Zhu, W., Wei, X., Li, S., Huang, Y., Liu, M. & Lin, X. 2016. miR-22 contributes to the pathogenesis of patients with coronary artery disease by targeting MCP-1: An observational study. *Medicine (Baltimore)*, **95**: 44-18.

Chen, P.M., Shibata, R., Zidovetzki, M., Fisher, B.V., Zlokovic, F.M. 2012. Endothelin-1 and monocyte chemoattractant protein-1 modulation in ischemia and human brain-derived endothelial cell cultures. *Journal of Neuroimmunology*, **116 (1)**:62-73.

Chrysant, S.G. 2019.The current status of homocysteine as a risk factor for cardiovascular disease: A mini review. *Expert Rev. Cardiovasc. Ther*., **16**:559–565.

Connie, W.H., Woo, Y. L., & Karmin, O. 2017. Homocysteine Induces Monocyte Chemoattractant Protein-1 Expression in Hepatocytes Mediated via Activator Protein-1 Activation. *THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL*., **283(3)**: 1282–1292

De Lemos, J.A., Morrow, D.A., Blazing, M.A., Jarolim, P., *et al.* 2017. Serial measurement of monocyte chemoattractant protein-1 after acute coronary syndromes: Results from the A to Z trial. *J. Am. Coll. Cardiol* ., **50:** 2117–2124.

Djurovic, Z., Jovanovic, V., Obrenovic, R., Djurovic, B., Soldatovic, I., Vranic, A., Jakovljevic, V., Djuric, D., Zivkovic, V. 2021. The importance of the blood levels of homocysteine, folate and vitamin B12 in patients with primary malignant brain tumors. *J. BUON*., **25**:2600–2607

Dragomir, E. & Simionescu, M. 2016. Monocyte chemoattractant protein-1 – a major contributor to the inflammatory process associated with diabetes. *Arch. Physiol. Biochem*., **112**: 239–244

Elizabeth, A., Varga, M., Amy, C., Sturm, M.S., Caron, P., Misita Pharm, D., Stephan, M. M. 2016. Homocysteine and MTHFR Mutations Relation to Thrombosis and Coronary Artery Disease. *Circulation*, **111**:289-293.

Faeh, D., Chiolero, A., Paccaud, F. 2016. Homocysteine as a risk factor for cardiovascular disease: should we (still) worry about it?*Swiss Med Wkly*., **136**:745–56.

Feng, S.D., Jiang, Y., Lin, Z.H., Lin, P.H., Lin, S.M., Liu, Q.C. 2018. Diagnostic value of brain natriuretic peptide and β-endorphin plasma concentration changes in patients with acuteleft heart failure and atrial fibrillation. *Medicine (Baltimore).*, **96(34)**:75-26.

França, C.N., Izar, M.C., Hortêncio, M.N., do Amaral, J.B., Ferreira, C., Tuleta, I.D., & Fonseca, F.A. 2017. Monocyte subtypes and the CCR2 chemokine receptor in cardiovascular disease. *Clinical science*., **131**:1215-1222

Fujiwara, Y., Mikami, C., Nagai, M., Yamamoto, C., Hirooka, T., Satoh, M., Kaji, K. 2018. Homocysteine Inhibits Proteoglycan Synthesis in Cultured Bovine Aortic Smooth Muscle Cells. *Journal of health science*, **54(1)**:56-65.

Georgakis, M.K., Malik, R., Björkbacka, H., *et al*. 2019. Circulating monocyte chemoattractant protein-1 and risk of stroke: meta-analysis of population-based studies involving 17 180 individuals. *Circ Res*., **125(8)**:773-782

Gilbert, J., Lekstrom-Himes, J., Donaldson, D., Lee, Y. Hu, M., Xu, J., Wyant, T., Davidson, M. 2011. Effect of CC chemokine receptor 2 CCR2 blockade on serum C-reactive protein in individuals at atherosclerotic risk and with a single nucleotide polymorphism of the monocyte chemoattractant protein-1 promoter region. *Am. J. Cardiol*., **107**: 906–911.

Gruzdeva, O., Uchasova, E., Dyleva, Y., Akbasheva, O., Matveeva, V., Karetnikova, V., Kokov, A., & Barbarash, O. 2017. Relationship key factor of inflammation and the development of complications in the late period of myocardial infarction in patients with visceral obesity. *BMC cardiovascular disorders*, **1**7:36-53.

Guo, J., Gao, Y., Ahmed, M. *et. al*. 2022. Serum Homocysteine Level Predictive Capability for Severity of Restenosis Post Percutaneous Coronary Intervention. *Front. Pharmacol*., **13:**812-603.

Henzel, J., Kepka, C., Kruk, M., Makarewicz-Wujec, M., Wardziak, Ł., Trochimiuk, P., Dzieli ´nska, Z., Demkow, M. 2021. High-Risk Coronary Plaque Regression after Intensive Lifestyle Intervention in Nonobstructive Coronary Disease: A Randomized Study. *JACC Cardiovasc. Imaging.*, **14**: 1192–1202.

Ikeda, U., *et al.* 2020. Monocyte Chemoattractant Protein-1 and Coronary Artery Disease. *Clin. Cardiol*., **25**:143–147.

Isaksen, K., Halvorsen, B., Munk, P.S., Aukrus,t P., Larsen, A.I. 2020. Effects of interval training on in-flammatory biomarkers in patients with ischemic heart failure. *Scand Cardiovasc J* ., **53**: 213-219.

Jayedi, A., Zargar, M.S. 2019. Intake of vitamin B6, folate, and vitamin B12 and risk of coronary heart disease: A systematic review and dose-response meta-analysis of prospective cohort studies. *Crit. Rev. Food Sci. Nutr*., **59**:2697–2707.

Kim, J., Kim, H., Roh, H., Kwon, Y. 2018. Causes of hyperhomocysteinemia and its pathological significance. Arch. Pharm. *Res*., **41**:372–383.

Liu, B.H., Li, Y.G., Liu, J.X., Zhao, X.J., Jia, Q., Liu, C.L., Xu, Z.G., 2019. Assessing inflammation in Chinese subjects with subtypes of heart failure: an observational study of the Chinese PLA Hos-pital Heart Failure Registry. *J Geriatr Cardiol*., **16**: 313-319.

Makarewicz-Wujec, M., Henzel, J. *et al*. 2022. Usefulness of MCP-1 Chemokine in the Monitoring of Patients with Coronary Artery Disease Subjected to Intensive Dietary Intervention: A Pilot Study. *Nutrients*., **13**: 3047.

Moskalik, A., Niderla-Bielińska, J. & Ratajska, A. 2022. Multiple roles of cardiac macrophages in heart homeostasis and failure. *Heart Fail Rev.*, **27**:1413–1440.

Namiki, M., Kawashima, S., Yamashita, T., Ozaki, M., Hirase, T., Ishida, T., Inoue, N., Hirata, K.I., Matsukawa, A., Mor-ishita, R., *et al*. 2022.Local overexpression of monocyte chemoattractant protein-1 at vessel wall induces infiltration of macrophages and formation

of atherosclerotic lesion: Synergism with hypercholesterolemia. *Arterioscler. Thromb. Vasc. Biol*., **22:**115–120

Paganelli, F., Mottola, G., Fromonot, J., Marlinge, M., Deharo, P., Guieu, R., Ruf, J. 2021. Hyperhomocysteinemia and cardiovascular disease: Is the adenosinergic system the missing link? *Int. J. Mol. Sci*., **22**:16-30.

Pang, X., Liu, J., Zhao, J., Mao, J., Zhang, X., Feng, L. *et al.* 2018.Homocysteine induces the expression of C - reactive protein via NMDAr-ROS-MAPK-NF-κB signal pathway in rat vascular smooth muscle cells. *Atherosclerosis,* **236**:73–81.

Piek, A., Du, W., de Boer, R.A. & Silljé, H.H.W. 2019. Novel heart failure biomarkers: why do we fail to exploit their potential? *Crit Rev Clin Lab Sci*., **55(4)**:246-263

Popović, B.V. 2021.Understanding advanced statistical methods. *Journal of Applied Statistic.* **41(12)**:27-77.

Ridker, P.M., MacFadyen, J.G., Glynn, R.J., Bradwin, G., Hasan, A.A., Rifai, N. 2020. Comparison of interleukin-6, Creactive protein, and low-density lipoprotein cholesterol as biomarkers of residual risk in contemporary practice: a secondary analysis from the Cardiovascular Inflammation Reduction Trial. *Eur Heart J*, **41**:2952–61

Shenov, V., Mehendale, V., Prabhu, K., Shetty, R., Rao, P. 2017.Correlation of serum homocysteine levels with the severity of coronary artery disease.*Ind J Clin Biochem*., **29(3)**:339–44.

Soufer, R., Fernandez, A.B., Meadows, J., Collins, D., Burg, M.M. 2016. Body mass index and risk for mental stress induced ischemia in coronary artery disease. *Mol Med*, **22**: 286-291

Sreckovic, B., Sreckovic, V.D., Soldatovic, I., Colak, E., Sumarac-Dumanovic, M., Janeski ,H., Janeski, N., Gacic, J., Mrdovic, I. 2019. Homocysteine is a marker for metabolic syndrome and atherosclerosis. *Diabetes Metab. Syndr. Clin. Res. Rev*., **11**:179–182.

Stumpf, C.C., Lehner, D., Raaz, A., Yilmaz, T., Anger,W.G., Daniel, C.D., Garlichs, M. 2022. Platelets contribute to enhanced MCP-1 levels in patients with chronic heart failure. *Heart failure and cardiomyopathy,* **94(12)**: 1-16.

Tamura, Y., Sugimoto, M., Murayama, T., Ueda, Y., Kanamori, H., Ono, K., Ariyasu, H., Akamizu, T., Kita, T., Yokode, M. & Arai, H, 2008. Inhibition of CCR2 ameliorates insulin resistance and hepatic steatosis in db/db mice. Arterioscler. *Thromb. Vasc. Biol*., **28**: 2195–2201.

Uzelac, J.J., Djukic, T., Radic, T., Mutavdzin, S., Stankovic, S., Rakocevic, J.K., Borovic, M.L. *et al.* 2021. Folic acid affects cardiometabolic, oxidative stress, and immunohistochemical parameters in monocrotaline-induced rat heart failure. *Can. J. Physiol. Pharmacol*., **98**:708–716.

Vasan, R.S., Beiser, A., D'Agostino, R.B., *et al.* 2020, Plasma homocysteine and risk for congestive heart failure in adults without prior myocardial infarction. *JAMA*., **289**: 1251-1257.

Ventura, P., Panini, R., Verlato, C., Scarpetta, G., Salvioli, G. 2017. Hyperhomocysteinemia and related factors in 600 hospitalized elderly subjects. *Metabolism.,* **50**: 1466-1471.

Weber, K.S., Nelson, P.J., Grone, H.J., Weber, C. 2010. Expression of CCR2 by endothelial cells: Implications for MCP-1 mediated wound injury repair and in vivo inflammatory activation of endothelium. *Arterioscler Thromb Vasc Biol*., **19**:20-85.

Wilson, E.M., Diwan, A., Spinale, F.G. & Mann, D.L. 2014. Duality of innate stress responses in cardiac injury, repair, and remodeling. *J. Mol. Cell. Cardiol*., **37**:801–811.

Xie, R., Jia, D., Gao, C., Zhou, J., Sui, H., Wei, X., *et al*. 2019. Homocysteine induces procoagulant activity of red blood cells via phosphatidylserine exposure and microparticles generation. *Amino Acids*, **46:**1997–2004.

Yang, Q., He, G.W. 2020. Imbalance of homocysteine and H2S: Significance, mechanisms, and therapeutic promise in vascular injury. *Oxid. Med. Cell. Longev*., **10(123)**:762-9673.

Zhang, S., Yong-Yi, B., Luo, L.M., Xiao, W.K., Wu, H.M., Ye, P. 2017. Association between serum homocysteine and arterial stiffness in elderly: a community-based study. *J Geriatr Cardiol* ., **11**:32–8.