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The Relationship Between Homocysteine, Dopamine and Folic Acid in Serum of Patients with Cardiovascular Disease in Nassiria Governorate

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Abstract

Objectives: Cardiovascular diseases(CVDs) which include ischemic heart disease, stroke, heart failure, peripheral arterial disease, and several other cardiac and vascular illnesses, are the world's leading cause of mortality and significantly lower life expectancy. The research targeted at regulation of homocysteine metabolism has the potential to improve the quality of life and health span. The research also included measuring and evaluating dopamine and vitamin B9 for cardiovascular patients. Methods: This study was conducted at Nasiriya Heart Center ,Nasiriya General Hospital and Biochemistry Laboratory in the College of science University of Thi-Qar in the period between (October ,2022 to March, 2023) . In formed oral consent was taken for patients. The study included 88 men and women, 38control subjects and 50 patients their ages were between 40 − 70 years. The subjects were divided into two groups: 1. Control group: included (38) supposed approximately healthy subject,2. Patients group: included (50) patients with Heart disease. Excluded cases from this: Kidney diseases, Liver failure, Thyroid diseases Immunological diseases, Urinary tract infections, Acute joint diseases Pregnant women, Diabetes. Results : There was a significant increase in homocysteine concentration in the blood serum of the patients group compared to the control group. Significant decrease in the level of vitamin B9 and dopamine in the serum of patients compared to the control group. Conclusions: The study indicated a significant decrease in dopamine levels in cardiovascular patients, offset by an increase in homocysteine levels, which is considered a risk factor in cardiovascular patients. In addition, folic acid levels decreased in cardiovascular patients, and this contributed to the rise in homocysteine through the negative relationship between homocysteine and folic acid.

Keywords
Cardiovascular diseases, Dopamine, Homocysteine, Folate

Cardiovascular diseases (CVDs) which include ischemic heart disease, stroke, heart failure, peripheral arterial disease, and several other cardiac and vascular illnesses, are the world's leading cause of mortality and significantly lower life expectancy (Mensah et al., 2019).
The heart functions as a pump, and blood vessels are pathways for blood and cells that deliver oxygen and nutrients to sustain the molecular processes required for vascular development and the functionality of various tissues (Paganelli et al., 2021). There are two categories of CVD risk factors: modifiable and non-modifiable. Age, gender, ethnicity, and genetic characteristics are a few examples of risk variables that cannot be changed.

Modifiable risk variables include body mass, hypertension, fatty acid and lipoprotein levels, and smoking behavior. Health-promoting practices can help prevent or reduce modifiable risk factors. Exercise, a healthy diet, taking medicine, and quitting smoking can all lower a person's chance of having CVD (mes & Lewis, 2014). Although women typically have a lower incidence of CVD than males, a number of clinical evidences have shown that women have a greater rate of death and worse prognosis after an acute cardiovascular (CV) event (Gao et al., 2019). Cardiovascular complication rates are decreasing in the context of multifactorial risk reduction with statins and other lipid-lowering medications, antihypertensive treatments, and antihyperglycemic treatment approaches, but they continue to be higher for patients with diabetes mellitus than for those without (Low Wang et al., 2016).

Dopamine is a neurotransmitter, which is a chemical produced by neurons and released in ways that influence the activity of other neurons. It is sometimes classified as a neuromodulator (a type of neurotransmitter) because it acts to modulate the sensitivity to other neurotransmitters rather than substituting for them (Wise & Robble 2020). Dopamine plays critical roles in the regulation of learning, motivation, and movement. Understanding the information conveyed by dopamine is essential for determining how dopamine regulates various functions (Kim et al., 2020).While dopamine was first synthesized in 1910, it wasn't until the mid-1950s that it became recognized as a substance in its own right, rather than just an intermediary in the formation of noradrenaline (Marsden 2006). Dopamine is predominantly produced in the central nervous system (CNS), while the adrenal medulla also produces a small amount of it. In several non-neuronal tissues, such as the anterior pituitary and the pancreas, dopamine can also be found(Ben-Jonathan & Hnasko 2001).

Dopamine is a biogenic monoamine that belongs to the "catecholamines" family of neurotransmitters, which includes several related neurotransmitters such as dopamine, norepinephrine(noradrenaline),and epinephrine(adrenalin).These neurotransmitters, along with serotonin(5-HT), which is also a biogenic monoamine but belongs to a group called "indolamines" (Lipner et al., 2017).

Homocysteine is a sulfur-containing, nonprotein, toxic amino acid found in the interconversion pathway of methionine and cysteine. Homocysteine is broken down into two pathways: remethylation and trans-sulfuration (Hasan et al., 2019). Approximately 80% of plasma homocysteine is protein bound. Only a small amount exists as free reduced homocysteine, as the majority of the unbound portion is oxidized to form diamers (homocystine) or combined with cysteine tides (Thambyrajah & Townend 2000).

Blood tests are used to measure homocysteine concentrations. Between 4.4 and 10.8 mol per liter of blood, homocysteine levels are considered normal. Hyperhomocysteinemia is the medical term for abnormally high blood homocysteine levels that are above 15 mol/L. When people lack folic acid, vitamin B_6 , or vitamin B_{12} , their plasma homocysteine levels rise (Rujaswini et al., 2018).In relation to cardiovascular illness, homocysteine has received a lot of research attention, and it has been identified as a possible risk factor for stroke, coronary vascular disease, ischemic heart disease, and other vascular occlusive diseases (Jun Xu et al., 2018). It is now widely accepted that there is a link between Hcy and neurological issues like depression, Parkinson's disease, and Alzheimer's disease. It has also been demonstrated that 10% to 30% of Parkinson's disease patients have elevated plasma tHcy levels (Hannibal & Blom 2017). Hyperhomocysteinemia produces hypertension and cardiovascular disease is through homocysteine mediated damage to vascular smooth muscle and endothelial cells. This damage, in turn, leads to a loss of arterial vasodilation, vascular integrity, and thus increased blood pressure (BP) and accelerated atherosclerosis (Marwa & Mohammed 2022). Its name, homocysteine, derives from the fact that it shares chemical properties with cysteine. Endothelial cell destruction, a reduction in vascular flexibility, and modifications to the hemostasis process are thought to be caused by homocysteinemia. Homocysteine levels that are higher could intensify the negative consequences

of risk factors like smoking, high blood pressure, and lipid metabolism as well as encourage the onset of inflammation(Mohammed et al., 2021).

Vitamin B_9, folate, is a member of the family of water-soluble B vitamins. Folic acid is the type of folate that is present in fortified foods and nutritional supplements. The bioactive compound 5-methyltetrahydrofolate (5-MTHF) is generated in the liver by hepatic reductases 1, but folic acid itself is inactive in the human body (Ferrazzi et al., 2020).

It is found naturally in a wide variety of foods, including vegetables, fruits, nuts, beans, dairy products, meats, eggs, seafood, and grains. However, only approximately 50% of the folate naturally present in food is bioavailable (Riyam & Mohammed 2017).

Folic acid's chemical name is $CH_{19}N_7O_6$. The term "folates" refers to folic acid as well as its dihydro, tetrahydro, methyl, and formyl derivatives, which have metabolic activity (Shulpekova et al., 2021). Folate, an important nutrient crucial to the operation of various vital cellular processes, serves as a family of metabolic cofactors involved in 1-carbon transfer activities, cellular methylation reactions, amino acid metabolism, and nucleotide biosynthesis (Maruvada et al., 2020). Since folate protects megaloblastic anemia, neural tube birth abnormalities, cardiovascular disease, dementia, changes in cognitive function, osteoporosis, and numerous types of cancer, it is widely established that adequate folate intake is crucial for human health (Acosta-Elias & Espinosa-Tanguma 2020). The amino acid homocysteine levels in the blood are managed by vitamin B_9 in conjunction with vitamins B_6 and B_{12} and other minerals. Heart disease is linked to high homocysteine levels. Folic acid can regulate excessive homocysteine levels by remethylating homocysteine to methionine via methionine synthetase with vitamin B_{12} acting as a cofactor (Mahmood, L. 2014).

Materials and Methods

Study design

This study was conducted at Nasiriyah Heart Center , Nasiriyah General Hospital and Biochemistry Laboratory in the College of science University of Thi-Qar in the period between (October ,2022 to December, 2022) .The study included 88 men and women, 38control subjects and 50 patients their ages were between 40 − 70 years.

The subjects were divided into two groups:

1. Control group: included (38) supposed approximately healthy subject.
2. Patients group: included (50) patients with Heart disease.

Excluded cases from this: Kidney diseases, Liver failure, Thyroid diseases Immunological diseases, Urinary tract infections, Acute joint diseases Pregnant women, Diabetes.

Blood Sample collection

About (5ml) of blood was collected from men women by venous . Placed in a gel tube to separate the serum. The blood was allowed to clot at room temperature , and then the serum was separated by centrifugation (10 min at 3000 xg) the serum samples was removed and stored at (-20°C) for later measurement biochemical parameters, unless used immediately.

The statistical analysis

All statistitrnhjyuj8cal analysis was performed using SPSS, Windows version 23.0 software and Microsoft Excel 2010. The results were expressed as mean± standard deviations (mean ± SD) ,and Least Significant Difference (LSD). One - way analysis of variance (ANOVA) was used to compare parameters in different studied groups. P-values ($P< 0.001$) were considered statistically significant. Person correlation coefficient (r) is used to measure the strength at a linear association between two variables (r=+1) ,(r=-1) . Person correlation coefficient (r) was used to test the correlation relationship among the different parameters in each patients group.

Results

Serum Dopamine Concentration

Table (1) show a significant decrease in the concentration of serum Dopamine in patients group in comparison with controls group. As per previous studies and medical recommendations, dopamine is used to increase the pumping power of the heart and blood flow in the kidneys. There are two families of dopamine (DA) receptors, called D1 and D2, respectively. The D1 family consists of D1- and D5-receptor subtypes and the D2 family consists of D2-, D3-, and D4-receptor subtypes. In cardiology, the therapeutic

benefits of DA agonists are noted in the treatment of heart failure. At low concentrations, the primary cardiovascular effect of DA is on the vascular D1-receptors. By stimulating adenylate cyclase and thus, increasing intracellular concentrations of cyclic AMP (cAMP), D1-receptor stimulation consequently leads to vasodilatation. Therefore, DA is particularly useful in the management of states of low cardiac output associated with compromised renal function such as cardiogenic shock. As the stimulatory effects on the circulation are generally considered beneficial, DA is often used as a drug for preservation of regional blood flow, and is given for prophylaxis of impairment of cardio-renal function and protection of splanchnic flow(Emilien et al., 1999).

A direct role for dopamine in the regulation of vascular contractibility is believed to contribute to changes in blood pressure. In addition to blood pressure modulation, dopamine inhibits the secretion of the procoagulant von Willebrand factor from human endothelial cells through its action on D2, D3, and D4 receptors. High levels of von Willebrand factor is a recognized risk factor for coronary heart disease(Rubн & Maechler 2010).

Since human platelets express both adrenergic and dopaminergic receptors, the high catecholamine levels may easier explain the association between depression and CVD. Basically, through platelet α2-adrenergic or dopaminergic receptors, they modulate thrombopoiesis, and platelet function. Low concentrations of catecholamines and dopamine potentiate the effects of other agonists (e.g., ADP, collagen, and thrombin) enhancing platelet aggregation, whereas at high concentrations are sufficient alone to induce human platelet aggregation, granule secretion, and release of platelet markers (e.g., Platelet Factor 4 (PF4) and β-thromboglobulin (BTG)) (Amadio et al., 2020).

Table (1): Serum Dopamine levels of control and patients groups

Mean Levels of Parameters According to study Groups		
Groups	No.	Dopa.(ng/m) Mean ± SD.
Patients	50	18.62±6.12
Control	38	49.23±15.63
P. value		< 0.001**

Homocysteine

Table (2) shows a significant increase homocysteine in blood serum concentration in the patients group compared with the control group. Studies have shown that there is a significant relationship between Hyperhomocysteinemia with cardiovascular illness and its side effects, such as heart attacks and strokes (Ganguly & Alam 2015).

Increased risk of serious adverse cardiovascular events is linked to elevated serum homocysteine levels through reduced nitric oxide generation and coronary microvascular dysfunction (Ahmad et al., 2020). Potential mechanisms of Hcy's negative effects include endothelial dysfunction and mortality, increased oxidative stress, inflammation, and altered collagen metabolism (Jin, N. et al., 2021). According to studies, Hcy and CHD are closely associated, and it can be used to diagnose CHD independently as a risk factor.As a result of homocysteine's toxic effects on vascular endothelial cells, which include endothelial damage and dysfunction, proliferation of vascular smooth muscle cells, disruption of the balance between coagulation and fibrinolysis, and induction of pre-thrombosis in the body, the body enters a state of pre-thrombosis (Zhang et al., 2022).

From the early evidence, Hcy not only impacts endothelial function to result in a prothrombotic environment, but also initiates an including the N-methyl-D-aspartate receptor (NMDAr), reactive oxygen species (ROS), extracellular signal-regulated kinase (ERK), and nuclear factor kappa B (NF-B) signal pathway, to cause an inflammatory response and speed up atherosclerosis in cardiovascular diseases (Zhao & Zhang 2021).

Table (2): Serum homocysteine levels of control and patients' groups

Mean Levels of Parameters According to study Groups		
Groups	No.	HCY (pmol/mL) Mean ± SD.
Patients	50	415.95±83.48
Control	38	83.17±22.17
P. value		< 0.001**

Serum Folic acid Concentration

Table (3) show a significant decrease in the concentration of serum folic acid in patients group in comparison with controls group.

Folic acid is essential for the production of numerous coenzymes in many metabolic processes, most notably for the synthesis of purines and pyrimidines, nucleoproteins, and for the maintenance of erythropoiesis. Tetrahydrofolate is the most effective type of folic acid. Elevated homocysteine, which is a sign of an elevated risk of developing arteriosclerosis, is associated with a lack of folate (Khan & Jialal 2018).

Folic acid has a vital role in human body, cell growth, and development through many reactions and processes that occur inside it, including histidine cycle, serine and glycine cycle, methionine cycle, thymidylate cycle, and purine cycle. Since the body becomes deficient in folic acid, all cycles will become ineffective and lead to many problems such as megaloblastic anemia, cancer, and neural tube defects and cardiovascular diseases (Mahmood 2014).

The key to treating hyperhomocysteinemia is to comprehend how folic acid and Hcy are biosynthesized. Although it has been determined that folic acid, B_{12}, and B_6 deficits lead to elevations in Hcy, folic acid treatment has demonstrated to dramatically lower Hcy compared to that of its B vitamin equivalents. Supplementing with 0.5−5.0 mg of folic acid can reduce Hcy levels by 25%, which may minimize the risk of cardiovascular disease (Kaye et al., 2020). Atherosclerosis risk factors include low levels of folate and high homocysteine levels. A folic acid deficit can encourage methylation, raise homocysteine levels, harm vascular endothelial cells, and encourage atherosclerosis. Folic acid (FA) is an antioxidant that can lessen the production of reactive oxygen species and can prevent heart dysfunction during ischemia (Tang et al., 2017).

Table (3): Serum Folic acid levels of control and patients' groups

Mean Levels of Parameters According to study Groups		
Groups	No.	Folate (pg/ml) Mean ± SD.
Patients	50	2246.71±660.76
Control	38	3157.55±921.10
P. value		< 0.001**

Conclusions

The study indicated a significant decrease in dopamine levels in cardiovascular patients, offset by an increase in homocysteine levels, which is considered a risk factor in cardiovascular patients. In addition, folic acid levels decreased in cardiovascular patients, and this contributed to the rise in homocysteine through the negative relationship between homocysteine and folic acid.

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