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STUDY TO DETERMINE THE RELATION OF SERUM HOMOCYSTEINE WITH CORONARY HEART DISEASE

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Abstract:

Background: *CAD is the leading cause of death. Many factors are responsible for causing CAD, but 5 to 10 percent of CAD patients have none of the known risk factors. Changing the risk factor is an integral part of managing patients at risk or at risk of cardiovascular disease. Doctors looking after patients with cardiovascular disease should be aware of new risk factors. There are important relationships between established and new risk factors, and a better understanding of new risk factors can shed light on the pathogenic mechanisms of established risk factors.*

Objective: *To investigate the relationship of homocysteine in patients with coronary heart disease.*

Study design: *A Case control study.*

Place and Duration: *In the Medicine and Cardiology department of Benazir Bhutto Hospital, Rawalpindi for one year duration from March 2019 to March 2020.*

Methods: *This study was performed in 50 CAD patients and 50 people as a control group. All patients underwent standard clinical examination and blood draw for lipid profile and total fasting serum homocysteine test. Pearson chi-square test was used to evaluate statistical significance. A P value of less than 0.01 indicates that it is quite meaningful and a value below 0.05 is significant.*

Results: *The threshold value of homocysteine used in this study was 17 micro mol / L. 43 patients (86%) in the case group showed high homocysteine and 12 patients (24%) in the control group showed homocysteine. increased. And here the p value is <0.001 and there is a relative risk of 19.45. It indicates that high homocysteine is statistically highly significant.*

Conclusion: *The relationship between hyperhomocysteinemia and CHD was significant. Homocysteine values were higher in smokers and hypertensive patients.*

Key words: *coronary heart disease, homocysteine.*

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INTRODUCTION:

Coronary artery disease (CAD) is currently the leading cause of death in the world. There are many factors for CAD, but some patients do not have any of the major known risk factors. Some CAD risk factors, such as age, gender and family history, cannot be changed, but others, such as high blood pressure, diabetes, smoking and hyperlipidemia, can be controlled[1-2]. It is noteworthy that between 5 and 10 percent of CAD patients have no known risk factors. Typical symptoms of CAD are angina, shortness of breath, palpitations and excessive sweating[3-4]. When it comes to physical examination in patients with CAD with diabetes and / or peripheral arterial disease, clinicians should look for signs of atherosclerotic disease elsewhere, such as abdominal aortic aneurysm, carotid murmur, and reduced lower extremity pulse[5-6]. Changing the risk factor is an integral part of the treatment of patients at risk or at risk of cardiovascular disease. In addition to established cardiovascular risk factors, clinical trials have shown over 100 other conditions that may be associated with an increased risk of cardiovascular disease. Doctors taking care of patients with cardiovascular disease should be aware of new risk factors. About 25% of patients with premature cardiovascular disease have no established risk factor. As a result of the reduction in morbidity and mortality associated with hypertension, smoking and dyslipidemia, the relative contribution of new risk factors to the overall burden of cardiovascular disease will increase. There are important relationships between established and new risk factors, and a better understanding of new risk factors can shed light on the pathogenic mechanisms of established risk factors[7-8]. Based on collected evidence, the Bethesda Conference in 1996 recognized left ventricular hypertrophy, hyperhomocysteinemia, excess lipoprotein (a), hypertriglyceridemia, hyperfibrinogenemia (among other thrombotic factors), and oxidative stress as potential CAD risk factors. Serum homocysteine is positively associated with coronary artery disease, deep vein thrombosis and the risk of pulmonary embolism and stroke. It is uncertain whether these relationships are causal. It is important to address the causality problem because folic acid in vitamin B may reduce serum homocysteine and increase the chance of simple and safe prevention. Reasonable mechanisms of homocysteine action should be tested to assess causal homocysteine, not the causative agent[9-10]. The most common and reasonable mechanism is oxidative damage and the proliferation of vascular smooth muscle cells. It is thought that most endothelial dysfunction attributed to homocysteine is primarily due to oxidative stress. It is also one of the proposed mechanisms of DNA damage and carcinogenicity. In many in vitro studies, homocysteine was able to induce proliferation of vascular smooth muscle cells, an effect attenuated by folic acid. By increasing vascular smooth muscle proliferation, the lumen of the artery narrows, often damaging coronary artery disease. The normal reference range for total plasma homocysteine is generally defined as the 2.5 to 97.5 percentile range for healthy individuals. The lower limit is usually 5 µmol / L, but the upper limit varies significantly between clinical laboratories. In addition, in different populations, the upper limit may be from 10 to 20 µmol / L depending on age (with increasing age with level), sex (higher in men than women), ethnic group. And dietary intake of folic acid. Instead of describing homocysteine levels as normal or abnormal, it may be more useful to consider homocysteine as a gradual risk factor for cardiovascular diseases such as cholesterol and C-reactive protein.

MATERIALS AND METHODS:

After getting Ethical committee clearance, this study was conducted in 50 patients with coronary heart disease above 16 years of age, of both sex and also included 50 age and sex matched people as a control group. Informed consent was obtained from all the participants.

Exclusion criteria: Patients with Renal impairment, Pregnancy, Hypothyroidism, Nephrotic syndrome, cancer and Patients on Drugs like Sodium Valproate, Carbamazepine, Cyclosporin, Methotrexate, Theophylline, Levodopa, Metformin, Estrogen (OCP), INH, Fibrates and Niacin were excluded. All patients (cases and controls) underwent a standard clinical examination by nurses and physicians, which included anthropometry (height, weight, waist-hip ratio), blood pressure, and a blood drawn after six weeks of acute coronary event, for Basic Biochemical Analyses and Fasting total cholesterol, HDL-C, LDL- C, and triglycerides. Patients also received dietary and smoking counselling when necessary. Individuals also completed a questionnaire that incorporated numerous risk related issues, including a history of hypertension, family history, cholesterol medication use, and diabetes (ever treated or diagnosed by a physician), and, in women, menopausal status and use of hormones. Patients were classified as either never- or ever-smokers. Hypertension was defined as a blood pressure above 140/90 mm Hg, a history of hypertension, or the use of antihypertensive medications. Diabetes mellitus was diagnosed if the patient was using insulin or an oral hypoglycemic agent or reported a history of diabetes mellitus.

tHcy Assay: Total fasting serum tHcy was measured on samples drawn on follow up visit. Serum tHcy has been shown to be '10% to 30% higher than plasma tHcy. A tHcy cut off point of 17 micro mol/L was used for all initial interaction

analyses, which is the 90th percentile of tHcy values obtained in the lab. The plasma homocysteine levels were calculated by using the (Bio-Rad kit) homocysteine microplate enzyme immunoassay. This is intended for the quantitative determination of L-homocysteine in human serum or plasma. Venous blood samples were taken from the study population by trained physicians or nurses from an elbow vein. Blood was transferred to containers containing EDTA for homocysteine and lipoprotein analysis. Within 15 minutes after collection, platelet plasma was obtained by centrifugation at 3000 rpm for 15 minutes at room temperature and then transferred to a -80 ° C freezer. In groups at the end of the sample collection.

Comparison of risk factors in the case and control group was performed using the t test for equality of means. All values were calculated as mean ± standard deviation. The Pearson chi-square test was used to assess statistical significance. A P value below 0.01 indicates that this is very significant, and a value below 0.05 is important. This indicator is used to estimate relative risk.

RESULTS:

The case group is in the 34-85 age range and covers an average age of 55.96. The age range ranged from 34 to 70 in the control group, with an average age of 51.50. In the group of cases, 70% prevalence was observed in men, but this was not statistically significant. The homocysteine threshold used in this study was 17 micro mol / L. When 43 patients (86%) showed elevated homocysteine, and in the control group 12 patients (24%) showed elevated homocysteine. The Pearson chi-square test was used to assess statistical significance. And here the p-value is <0.001 with a relative risk of 19.45. It shows that elevated homocysteine is statistically very significant. LDL-C values above 130 mg / dL were observed in 18 patients (36%) compared to 1 (2%) in the control group. A value of 100 to 129 mg / dL was observed in 23 (46%) compared to 31 (62%) in the control group. A value of 90 to 99 mg / dL was observed in 3 (6%) compared to 12 (24%) in the control group. A value less than 90 mg / dL was observed in 6 (12%) compared to 6 (12%) in the control group. The average LDL-C value is 122.64 in the case group and 106.48 in the control group. The T test for mean equality has a p value of <0.001 and is very significant. HDL-C values below 40 mg / dL were observed in 28 patients (56%) in the case group compared to 35 (70%) in the control group. A value of over 40 mg / dL was observed in 22 (44%) compared with 15 (30%) in the control group. The average HDL-C value is 39.10 in the case group and 38.88 in the control group. The T test for equality means that the p-value is 0.842 and is not significant. The average total cholesterol in the case group is 160.34 mg / dl and 171.98 in the control group. And the relationship between the two is not statistically significant.

Table: 1Comparison of Homocysteine between Case and Control Group

		Group		
		Case	Control	Total
HCY <17	Count	7	35	45
	% with In HCY	15.6	84.4	100
	% with In GROU	14	76	45
HCY >17	Count	43	12	55
	% with In HCY	78.2	21.8	100
	% with In GROU	86	24	55
Total	Count	50	50	100
	% with In HCY	50	50	100
	% with In GROU	100	100	100
		Value	df	P value
Peasrson chi square		38.82	1	.000
N of valid cases		100		

The average triglyceride value in the case group is 115.52 mg / dl and 106.50 in the control group. The relationship between them is not important. In a family history, premature CHD occurred in 16 patients in the case group and 5 patients in the control group. Pearson's chi-square test has a p-value of 0.007 and the relationship is statistically significant. A sedentary lifestyle was present in 25 patients in the case group and 12 patients in the control group. The p-value is 0.007 and the relationship is statistically significant. In the group of cases, 19 patients (38%) were alcoholics compared to 12 (24%) in the control group. The P value is 0.130 and the relationship is not statistically significant. Diabetes occurred in 22 (44%) patients in the case group and 8 (16%) patients in the control group.

Table 2: Homocysteine in smokers and non-smokers

		Smoking		
		Case	Control	Total
HCY <17	Count	6	1	7
	% with In HCY	85.7	14.3	100
	% with In GROU	21.4	4.5	14
HCY >17	Count	22	21	43
	% with In HCY	51.2	48.8	100
	% with In GROU	78.6	95.5	86.0
Total	Count	28	22	50
	% with In HCY	56.0	44	100
	% with In GROU	100	100	100
		Value	df	P value
Peasrson chi square		11.79	3	0.017
N of valid cases		50		

The p-value is 0.002 and the relationship is statistically significant. 22 patients (44%) smoked in the case group and 13 (26%) in the control group. The p-value is 0.059, and the relationship is not statistically significant. Hypertension was present in 26 (52%) patients in the case group and 5 (10%) patients in the control group. The P value is <0.001, and the relationship is very important. In the case group 52% of patients had hypertension, and in the hypertensive population 86% had an increase in homocysteine, and the relationship between high homocysteine and hypertension was statistically significant at 0.023 P. In the case group 44% of patients smoked and 86% of homocysteine increased in this cigarette population. The p-value was 0.017, and the relationship between high homocysteine and smoking was statistically significant. Parameters such as age, lifestyle, early family history of coronary heart disease and BMI, and waist to hip ratio were not statistically related to homocysteine levels.

Table 3: Homocysteine in hypertensive and nonhypertensives

		Hypertension		
		Case	Control	Total
HCY <17	Count	5	2	7
	% with In HCY	71.4	28.6	100
	% with In GROU	20.8	7.7	14
HCY >17	Count	19	24	43
	% with In HCY	44.2	55.8	100
	% with In GROU	79.2	92.3	86
Total	Count	24	26	50
	% with In HCY	48	52	100
	% with In GROU	100	100	100
		Value	df	P value
Peasrson chi square		11.79	3	0.017
N of valid cases		50		

DISCUSSION:

The main risk factors are strongly associated with the development of CHD, along with high levels of LDL cholesterol. Although many of them are directly atherogenic, their ability to predict CHD is still limited. The most excessive risk of CHD can be explained by the main risk factors; this has been shown at very low risk in people with optimal levels of all these risk factors. However, when significant risk factors exist, they represent only half the risk variability of coronary artery disease; other factors that still need to be identified clearly show how much the major risk factors affect the absolute risk of coronary artery disease. One of them is hyperhomocysteinemia studied here[10-11]. As a result, extensive research was conducted to identify new risk factors that would increase predictive power in humans. These new factors can be called emerging risk factors. Serum homocysteine elevation correlates positively with CHD risk. The mechanism

of the relationship between homocysteine and CHD is not well understood, but people with hereditary forms of severe homocysteinemia have early vascular damage and atherosclerosis[12]. In any case, the strength of the relationship between homocysteine and CHD is not as great as the strength of the major risk factors. Also, an increase in homocysteine levels is not as common as a major risk factor. For these reasons, ATP III does not mention high homocysteine as an important risk factor for changing low-density lipoprotein cholesterol targets. While homocyte growth is not classified as an important risk factor, some researchers claim that the association with CHD is strong enough to make it a direct treatment target. The current intervention for high homocysteine was perhaps dietary folic acid in combination with other B vitamins (B6 and B12). Various clinical trials are underway to assess whether lowering homocysteine will reduce the risk of coronary heart disease. ATP III does not recommend routine measurement of homocysteine as part of a risk assessment to change LDL cholesterol target levels for primary prevention[13]. This lack of recommendations is based on uncertainty about the strength of the relationship between homocysteine and CHD, the lack of clinical studies showing that additional vitamin B will reduce the risk of CHD. However, homocysteine measurement remains an option, for example in selected cases with a strong family history of early ischemic heart disease in a low-risk patient. If raised, the preferred clinical approach according to ATP III is to determine vitamin B12 levels and, if normal, ensure adequate intake of folic acid instead of changing the target LDL cholesterol level. In in vitro models, high levels of homocysteine caused hypercoagulability by reducing thrombomodulin levels, protein C activity and heparin sulfate levels, as well as by preventing tissue plasminogen activator binding to endothelial cells. . In addition, they increased factor V and XII, tissue factor expression in endothelial cells, and induced platelet aggregation and adhesion. In clinical studies, hyperhomysteinemia was associated with the activation of coagulation systems in patients with early atherosclerosis and thrombin production in patients with acute coronary syndrome[13]. Hyperhomocysteinemia has also been found to be an independent risk factor for VTE. In addition, homocysteine induces the expression and release of inflammatory monocyte chemotactic proteins in human monocytes and endothelial cells from chemotactic monocyte protein 1, vascular cell adhesion molecule 1 and interleukin 8, which leads to increased adhesion. Exposure of T cells and monocytes to endothelial cell homocysteine. The thrombotic and proinflammatory effects of high levels of homocysteine may explain that the risk of recurrent coronary events increases in patients with high levels of homocysteine, regardless of the degree of underlying coronary artery disease. ATP III does not recommend routine measurement of homocysteine as part of a risk assessment to change LDL cholesterol target levels for primary prevention. This lack of recommendations is based on uncertainty about the strength of the relationship between homocysteine and CHD, the lack of clinical studies showing that additional vitamin B will reduce the risk of CHD. However, homocysteine measurement remains an option, for example in selected cases with a strong family history of early ischemic heart disease in a low-risk patient[14]. If raised, the preferred clinical approach according to ATP III is to determine vitamin B12 levels and, if normal, ensure adequate intake of folic acid instead of changing the target LDL cholesterol level. In in vitro models, high levels of homocysteine caused hypercoagulability by reducing thrombomodulin levels, protein C activity and heparin sulfate levels, as well as by preventing tissue plasminogen activator binding to endothelial cells. In clinical studies, hyperhomysteinemia was associated with the activation of coagulation systems in patients with early atherosclerosis and thrombin production in patients with acute coronary syndrome. Hyperhomocysteinemia has also been found to be an independent risk factor for VTE. In addition, homocysteine induces the expression and release of inflammatory monocyte chemotactic proteins in human monocytes and endothelial cells from chemotactic monocyte protein 1, vascular cell adhesion molecule 1 and interleukin 8, which leads to increased adhesion. Exposure of T cells and monocytes to endothelial cell homocysteine. The thrombotic and proinflammatory effects of high levels of homocysteine may explain that the risk of recurrent coronary events increases in patients with high levels of homocysteine, regardless of the degree of underlying coronary artery disease. However, it is still unknown whether high homocysteine causes or is a consequence of cardiovascular disease. The addition of folic acid and other B vitamins to the diet effectively lowers levels, but whether or not it improves clinical outlook is also uncertain and is the subject of several ongoing clinical trials. On the other hand, there is good reason to believe that homocysteine is an independent cardiovascular risk factor and that homocysteine-lowering treatment may ultimately have little clinical benefit[15]. Treatment with 0.4-5.0 mg / day or vitamin B12 0.5-1.0 mg / day or both is inexpensive and probably safe and may be cost-effective in preventing cardiovascular events if reduction therapy is confirmed by ongoing studies trials. Homocysteine is preferred. Even if there is no clear evidence of clinical benefit, the selection and treatment of hyperhomocysteemia in selected patients (i.e. patients with an early history of cardiovascular disease, stroke or venous thromboembolism or other current risk factors) can

be justified. In these cases, treatment is unlikely to hurt and can provide significant benefits. In this study, the relationship between hyperhomocysteinemia and other emerging risk factors, such as lipoprotein A and hs-CRP, was not analyzed. This is a limitation of this study.

CONCLUSION:

The relationship between hyperhomocysteinemia and CHD was significant. Homocysteine values were higher in smokers and hypertensive patients. Established risk factors such as hypertension, diabetes, LDL-C, and family history of CHD were higher in patients than in the control group. Smoking and low HDL-C were not significantly associated with CHD.

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