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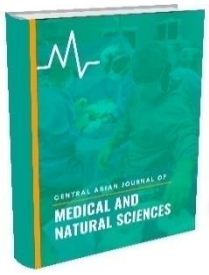

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A novel Cardiovascular Risk Marker Among Young Adults' Patient with Coronary Artery Disease in Basra Province

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Abstract: Background; Despite the absence of classic CVD risk factors, patients still have CVD events, prompting the quest for novel markers of CVD risk. Given inflammation's central involvement in atherosclerosis, inflammatory biomarkers have emerged as promising indicators. Particularly useful in predicting cardiovascular risk across a wide range of patient populations are measures of C-reactive protein (CRP), Leptin, and ceruloplasmin. Higher levels of hs Crp and Leptin were found in patients with CVD compared to controls, although ceruloplasmin showed no statistically significant differences.

Methodology: The study comprised 90 patients diagnosed by coronary angiography. Participants in this study (53 males and 37 females) with CAD, their ages ranged from 25-45 years, the patient and control who attended Al-Sadr Teaching Hospital and Naft Al-Basra Specialized Heart Hospital, Basra, Iraq between from December 2022 to the end of September 2023 in Basrah, Southern Iraq. Leptin was measured using an (ELISA). hsCrp.ceruloplasmin was also measured using an Cobas e411.

Results; Leptin, hsCrp levels were significantly higher in patients compared to age-matched healthy controls, ceruloplasmin levels were non significantly between patients compared to age-matched healthy controls, according to the current study.

Conclusions: From our results, we can conclude the relashinship between leptin, hsCrp and ceruloplasmin levels and coronary artery disease Basra Governorate.

Key words: C. rective protein, cardiovascular disease, biomarkers, coronary artery disease.

Introduction

Heart and artery problems are at the root of cardiovascular disease (CVD). Angina, coronary events, stroke, heart failure, hypertension, rheumatic fever, cardiomyopathy, arrhythmias, valvular heart disease, congenital heart disease, aortic aneurysms, peripheral artery disease, thromboembolic disease, and venous thrombosis are all examples of cardiovascular diseases.[1]

Diseases can evolve in a variety of ways. 53% of all CVD deaths can be attributed to dietary causes.Atherosclerosis is the root cause of cardiovascular disease, stroke, and peripheral artery disease.Factors include smoking, diabetes type 2, obesity, lack of exercise, high cholesterol, poor nutrition, alcohol abuse, and sleep deprivation. High blood pressure (13%), tobacco use (9%), diabetes (6%), inactivity (6%) and obesity (5%) are the primary causes of death from cardiovascular disease.[2]

Endothelial dysfunction, immunology, inflammation, and dyslipidemia all play a role. Fatty streak, a hallmark of atherosclerotic plaque, may result from several situations; changeable procedure that might begin in early childhood. Smooth muscle cells, extracellular matrix, and lipid-laden macrophages (foam cells) all contribute to the atheroma plaque's formation by intimal thickening, aggregation, and proliferation. Macrophage recruitment due to deep layer apoptosis during lesion progression has been linked to subsequent calcification and the development of atherosclerotic plaques. Atherosclerotic cardiovascular disease is slowed and sped up by arterial remodeling and intra-plaque hemorrhage, respectively.[4,5]

Atherogenesis is the leading cause of CVD. Location of arterial plaque buildup. These lesions may be made narrower by atheromatous plaque . Symptoms, if any, typically manifest in midlife, though they are typically absent during commencement. Heart disease, stroke, peripheral artery disease, and kidney problems are all possible outcomes of significant arterial damage.[6]

Angina, sometimes called angina pectoris, is a type of chest pain that occurs when the heart muscle isn't getting enough blood. typically indicative of coronary artery disease symptoms. When one or more of the arteries that provide blood to the heart muscle become narrowed or completely blocked, the result is angina. Atherosclerosis is the most common form of coronary artery disease and the major cause of coronary artery obstruction. Less common causes of angina include anemia, heart failure, and arrhythmias.[7]

Acute myocardial infarction occurs when blood supply to the heart is cut off. Lack of oxygen causes cardiac ischemia. Reduced coronary blood flow due to multiple factors. Thrombosis, which forms when an atherosclerotic plaque ruptures, reduces blood flow to the heart's coronary arteries. Inadequate oxygen delivery to the heart (myocardial ischemia) can also be caused by conditions such as coronary artery embolism (2.9%), cocaine-induced ischemia, coronary dissection, and coronary vasospasm.[8]

The effect of leptin on cardiovascular health is controversial. Leptin has been linked to chronic inflammation in numerous studies. Increased levels of leptin are associated with an increased risk of cardiovascular disease in the obese. Leptin is a nonimmunological biomarker for the progression of heart failure seen in patients with dilated cardiomyopathy.[9]

Liver-made enzyme ceruloplasmin (Cp) oxidizes nitric oxide (NO) to boost low-density lipoprotein oxidation and decrease NO bioavailability. Heart failure (HF) may result from the effects of endogenous NO secretion on cardiac contraction. Endothelial dysfunction and atherosclerosis are caused by oxidized low-density lipoprotein, which is a significant proatherogenic agent in arterial walls. High-sensitivity C-reactive protein (hs-CRP), leukocyte counts, and myeloperoxidase are all nonspecific inflammatory markers associated with cardiovascular disease (CVD), and Cp, an acute-phase reactant, is correlated with these variables as well. These observations suggest a link between Cp and CVD.[10,11]

Methodology

This is a case-control study included 90 patients diagnosed by coronary angiography were included Participants in this study (53 males and 37 females) with CAD, their ages ranged from 25-45 years. A control group of 90 healthy. 90 patients and control who attended Al-Sadr Teaching Hospital and Naft Al-Basra Specialized Heart Hospital, Basra, Iraq from December 2022 to the end of September 2023 in Basrah, Southern Iraq. We excluded children, patients aged above 55 and under 25 years. Blood samples for the measurement of serum Leptin, hsCrp and ceruloplasmin , A total of 5 ml of blood was drawn from each patient and control subject were placed in sterile gel tubes and allowed to coagulate at room temperature for 30 minutes before being centrifuged for 15 minutes at a speed of 3000 rpm to separate the components. The serum should be separated and kept at a temperature of -20 degrees Celsius until use. Leptin was assayed by an Enzyme linked immunosurbent assay (ELISA) according to the operational automated of Sunlog, China. hsCrp and ceruloplasmin was assayed by an Electrochemiluminescence assay according to the operational automated ofCobas e411, ROCHE, German.

Statistical Analysis

The statistically significant differences were determined using SPSS (version 26).

Results

Table (3-1) shows no significant sex distribution differences between healthy controls and patients (P= 0.88). The healthy and sick groups have similar age distributions (P= 0.92). In patients, (51) and (46) were smokers, while in controls, (39) and (44) were non-smokers, a non-significant difference (P=0.52). High hypertension rates in patients were significantly different from controls (P<0.01). Weight, Height, and BMI were not significantly different between healthy controls and patients (P= 0.335, 0.239, 0.125) in Table 3-1. The healthy and sick groups have similar physical activity status distributions (P= 926). Pharmaceutical history shows statistically significant differences between patients and controls for Statin, Aspirin, oral hypoglycemic medications, and Clopidogrel (P= 0.001). Beta blocker was not statistically significant between patient and control group (P= 0.06).

Table (1): Socio-demographic characteristics of the study population

Characteristic		Control group (n=90)	Patients group (n=90)	P. value
Male	No.	52	53	0.88
	%	57.8%	58.9%	
Female	No.	38	37	
	%	42.2%	41.1%	
Total	No.	90	90	
	%	100%	100%	
Age (year) Mean ± SD		39.41 ± 5.31	40.42 ± 4.28	0.92
Smoker	Yes	46	51	0.52
	No	44	39	
Hypertension	Yes	39	59	<0.01
	No	53	31	
Weight(kg) mean± SD		75.72±9.35	77.09±10.66	0.335
Height(m) mean± SD		1.62±0.08	1.60±0.06	0.239
BMI (kg/m2) mean± SD		28.94±4.09	29.84±4.10	0.125
Physical activity Status n(%)	Active	12(7.33)	14(6.14)	0.926
	Inactive	88	86	
Drug history n(%)	Statin	12(7.55)	16(5.62)	0.001
	Beta blocker	14(4.42)	15(6.02)	0.060
	Aspirin	33(2.72)	38(2.36)	0.001
	Oral hypoglycemic drugs	10(9.01)	15(6.02)	0.001
	Clopidogrel	21(4.28)	31(2.90)	0.001

*Chi Squared test: NS: Non significant at P>0.05, SD: Standard deviation

Table (2) showed a little significant decrease in the levels of ceruloplasmin in the patients group when compared to the control group (0.24±0.08 vs. 0.22±0.06, P<0.05). The table also showed a high significant increase (P<0.001) in each of leptin and CRP in the patients group compared to the control (3.75±0.92 vs. 4.22±0.84) (1.32±1.17 vs. 6.91±12.8) respectively.

Table (2) showed the deference in Leptin, Ceruloplasmin and CRP between control and patient group.

Parameters	Control group (n=90)	Patients group (n=90)	P. value
	Mean± SD	Mean± SD	
Leptin	3.75± 0.92	4.22± 0.84	<0.001
Ceruloplasmin	0.24± 0.08	0.22± 0.06	<0.05
CRP	1.32± 1.17	6.91± 12.8	<0.001

Table (3): As compared between patients groups (high risk and low risk patients), the table (3) show non-significant changes in the levels of leptin, ceruloplasmi, CRP.

Table (3): As compared between patients groups (high risk and low risk patients)

Parameters	High risk group (n=45)	Low risk group (n=45)	P. value
	Mean± SD	Mean± SD	
Leptin	4.00± 0.99	4.39± 1.63	0.19
Ceruloplasmin	0.24± 0.08	0.24± 0.07	0.95
CRP	7.92± 16.24	5.92± 8.36	0.58

Regarding lipid profile, table (4) show significant decrease in the serum levels of LDL in patients group as compare to the healthy control (84.84±32.94 vs. 68.09±27.24, P<0.05), while there is non-significant change in each of HDL, TG and VLDL.

Table (4): Comparison of lipid profile between control group and patients with CVD

Parameters	Control group (n=90)	Patients group (n=90)	P. value
	Mean ± SD	Mean ± SD	
HDL	30.60 ± 6.17	31.15 ± 8.31	0.77
LDL	84.84 ± 32.94	68.09 ± 27.24	<0.05

VLDL	**21.88 ± 12.47**	**21.88 ± 11.72**	**0.99**
TG	**109.45 ± 62.42**	**109.53 ± 58.54**	**0.99**

Table (5) show a significant decrease in serum levels of LDL in patients compared to control group (67.20 ± 23.27 vs. 84.26 ± 35.60, P<0.05), while there is non-significant difference in each of (HDL, VLDL and TG).

Table (5): Comparison of lipid profile between control group and patients with CVD according to male

Parameters	**Control group (n=52)**	**Patients group (n=53)**	**P. value**
	Mean ± SD	**Mean ± SD**	
HDL	27.95 ± 3.77	29.79 ± 6.95	**0.18**
LDL	84.26 ± 35.60	67.20 ± 23.27	**<0.05**
VLDL	24.57 ± 14.81	23.02 ± 12.14	**0.65**
TG	122.76 ± 74.05	116.77 ± 61.15	**0.09**

Discussion

When comparing Leptin,hsCRp between the control group and the patients, a significant increase in patients group compared to control (**3.75**±0.92 vs. 4.22±0.84, P=<0.001) (1.32±1.17 vs. 6.91±12.8, P<0.001) respectively, while there is a significant decrease in serum levels of Ceruloplasmin in patients group compared to control (0.24±0.08 vs. 0.22±0.06, P<0.05). When comparing age between the control group and the patients, a result show non significant (39.41 ± 5.31vs. 40.42 ± 4.28, P=0.33).

This result is agree with.[12] Patients with acute myocardial infarction had considerably greater levels of Leptin. Recent studies have shown that elevated leptin levels are linked to AMI, however there is not yet enough evidence to include leptin as a standalone risk factor for this condition. High serum leptin levels have also been linked to an increased risk of stroke, left ventricular hypertrophy, and chronic heart failure.[13]

Leptin's mechanism is poorly understood. Regarding AMI as an inflammatory condition, one mechanism has been extensively researched. TNF-, or tumor necrosis factor alpha, is a key pro-inflammatory mediator that has been related to increased mortality and recurrent myocardial infarction. Leptin normally has a suppressive effect on TNF- expression; however, there is mounting evidence that hyperleptinemia, particularly in obese individuals, can set off an inflammatory response by activating TNF- through the p38 and JNK (c-Jun N-terminal kinase) MAPK (mitogen-activated protein kinases)

pathway in adipose tissues. TNF- has also been linked to DM2 due to its role in insulin resistance in obese people. Examining leptin's function in atherogenesis provides insight into a different potential pathway. When leptin binds to its receptor Ob-R, which is mostly expressed in the hypothalamus but also in macrophages, endothelial cells, and smooth muscle cells, it sends a signal to these cell types. Plaque formation is a major contributor to cardiovascular disease because it triggers inflammation, dysfunctional endothelial cells, and smooth muscle migration to the wounded intima.[14,15]

This result is disagree with.[16] The blood leptin level did not vary significantly in the study of 122 AMI patients admitted to the ICU, however it was higher in patients who were overweight or had a high body mass index or waist circumference. The author draws the conclusion that high leptin levels are associated with obesity and high body mass index, which are in turn linked to cardiovascular disease.[17]

Ceruloplasmin (CP) is a plasma glycoprotein that, in healthy adults, binds 95% of the total circulating copper. Serum CP in adults is mostly synthesized in the liver, and its production is stimulated by proinflammatory agonists. This result is disagree with. correlation between elevated ceruloplasmin levels and higher danger of heart attack and stroke.[18]

Autoantibodies against oxidized LDL (anti-oxLDL) are formed when the atherosclerotic process is initiated or accelerated by the oxidation of Low-density lipoproteins (LDLs). Atherosclerotic lesions containing CP and other acute-phase proteins seem to implicate a mechanism involving lipid and lipoprotein oxidation in the genesis of CHD. deserves special attention because it's the only study showing a connection between anti-oxLDL levels and CP levels and copper levels in patients with CVD . In patients after endarterectomy, atherosclerotic process and restenosis were linked with serum amounts of CP and LDL lipid peroxides.[19]

Most studies show a positive correlation between serum CP and CHD, but this correlation has been called into question by others. The suppression of myeloperoxidase, a key enzyme in the generation of free radicals, was demonstrated by Chapman et al. to be yet another antioxidant characteristic of CP. These results do not agree with the results of our research.[20]

The relationship between C-reactive protein (CRP) and cardiovascular disease (CVD) has been studied extensively for many years. Cardiovascular disease (CVD) is an inflammatory disorder, and CRP is an acute phase protein. There is ongoing debate on whether or not CRP levels are linked to an increased risk of cardiovascular disease. Conventional wisdom holds that low-density lipoprotein cholesterol is the best predictor of cardiovascular disease. However, CRP may be a novel marker or new treatment target for CVD due to its distinctive properties. Clinical investigations have shown that CRP is a predictor of CVD, although it is unclear whether or not it plays a direct role in the etiology or progression of the disease. New clinical research suggests that reducing plasma CRP levels can lessen the occurrence of CVD. Consistent and roughly proportional relationships between CRP concentration and risk of cardiovascular disease, stroke, death from vascular causes, and mortality from a variety of malignancies and lung illness have been found. It's not entirely obvious how CRP is relevant to so many different diseases. Conventional risk factors and additional inflammatory indicators have significant

bearing on associations with ischemic vascular disease. These results is agree with the results of our research.[21]

Serum C-reactive protein detection may also predict coronary events in patients with stable or unstable angina. patients with unstable angina whose CRP plasma levels are monitored continuously after hospital discharge had an improved ability to predict the risk of future coronary events.[22]

As a result, CRP can foretell the gravity of CVD, and monitoring CRP levels may be an efficient means of preventing CVD. While CRP has been shown to be a predictive biomarker of inflammation in CVD, it is still uncertain if reducing CRP levels is beneficial in the treatment of CVD. Those who have suffered an acute myocardial infarction may benefit from long-term statin medication because it has been demonstrated to lower serum CRP levels. Patients' C-reactive protein levels were lowered by 37% when statins were used in the well-known The Case for Preventive Statin Use Reduced rates of cardiovascular disease were the result of the Jupiter statin study (JUPITER). Other clinical investigations have found the same thing.[23]

Although most studies showed that the high level of C-reactive protein was related to cardiovascular disease, there are some studies that have a different opinion, as their results do not agree with the results of our research.

People with heart disease and myocardial infarction often take anti-inflammatory drugs in addition to lipid treatments, and this helps bring their C-reactive protein levels down to normal or within the normal range.

When comparing the levels of leptin, ceruloplasmin, C-reactive protein (CRP) between high-risk and low-risk groups for cardiovascular disease (CVD), it is possible to find non-significant differences($P=0.19$, $P=0.95$, $P=0.58$, $P=0.65$) respecteviely. These biomarkers have been implicated in the development and progression of CVD, but their significance between these groups may vary for several reasons.

1. Sample Size: The size of the study population plays a crucial role in determining the statistical power to detect significant differences. If the sample size is small, the study may lack the power to detect true differences in biomarker levels between high-risk and low-risk groups. Increasing the sample size can help improve statistical power and increase the likelihood of discovering significant differences if they exist.

2. Heterogeneity within the Groups: The high-risk and low-risk groups may consist of individuals with varied characteristics and comorbidities that can influence biomarker levels independently of CVD risk. Factors such as age, sex, body mass index (BMI), smoking status, and other comorbidities may confound the association between these biomarkers and CVD risk. It is crucial to control for these confounding variables and consider subgroup analyses based on specific characteristics to obtain a more accurate understanding of the relationship.

3. Multifactorial Nature of CVD: Cardiovascular diseases are complex and influenced by multiple genetic, environmental, and lifestyle factors. Many biomarkers are associated with CVD risk, and their individual contribution to the development and progression of the disease can vary. Focusing solely on leptin, ceruloplasmin, and CRP levels may not capture the full complexity of CVD risk, leading to non-significant results. It is important to consider other relevant biomarkers and risk factors that collectively contribute to CVD risk.

4. Temporal Dynamics: Biomarker levels can vary throughout the day and in response to various stimuli. A single measurement of leptin, ceruloplasmin, or CRP may not fully represent an individual's overall status or risk for CVD. Longitudinal studies or repeated measures over a specific time period may be necessary to capture the dynamic nature of these biomarkers and their association with CVD risk.

Interpreting non-significant results should be done cautiously. Non-significance does not necessarily indicate the absence of an association between these biomarkers and CVD risk. It might reflect limitations in the study design, inadequate statistical power, or the complex nature of CVD pathogenesis. Further research, incorporating larger sample sizes, controlling for confounding variables, and considering additional biomarkers, is crucial to obtain a more comprehensive understanding of the relationship between leptin, ceruloplasmin, CRP, and CVD risk.

Despite non-significant differences, studying the role of these biomarkers in CVD is valuable. Leptin, ceruloplasmin, and CRP are involved in various physiological processes, including inflammation, oxidative stress, and lipid metabolism, which are relevant to CVD pathology. Exploring their mechanisms and potential interactions with other risk factors can provide insights into CVD development and may have implications for preventive strategies and targeted interventions in high-risk populations.

Conclusion

In conclusion, we can conclude from the results of the research that levels of leptin and C-reactive protein, in addition to ceruloplasmin, are considered risk factors in people with cardiovascular diseases, and an increase in these biomarkers can lead to health problems in people with heart problems.

Declaration

Ethical approval is Not applicable.
Consent to participate is Not applicable.
Consent for publication is Not applicable.
Competing interests, the authors declare no competing interests

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