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Role of C - Reactive Protein as an Inflammatory Marker in Patients with Coronary Artery Disease: A Case – Control Study in Erbil- Kurdistan Region of Iraq

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Abstract

Background and aim: Inflammation has been long regarded as a key contributor to atherosclerosis. Recent decades have provided extensive and mounting evidence concerning the pivotal interplay between inflammation and CAD, reinforcing the concept of inflammation not only as a risk marker but also as a risk factor for the development and progression of atherosclerotic disease. ***Methods****:* This was a case control study that has been enrolled among 404 patients, divided into two different groups (case-CAD patients and control group-Patients with Normal Coronary Angiography) that presented to Catheterization unit of Surgical Specialty Hospital- Cardiac Center/ Erbil City-Iraq from 1 Sept 2021 to 1 Jan 2022. ***Results****:* A total of 404 patients of case and control group was included from both genders, the mean age was 55.9 ±10.6, ranging from 30 to 77 years of age, based on their coronary angiographic profile 57.4% of them were Coronary Artery Disease cases and 42.6% were controls. (58.4%) of the study population were males and (41.6%) were females. The mean of CRP level amongst cases were higher (6.2 ± 10) than the controls (3.5 ± 4.7), and this was significant with a P = 0.022. In our study we found that Highly Sensitive-CRP was high amongst Case Group (Patients with CAD) by 70% while comparing to only 30% of Control group who had High CRP levels. And this was statistically significant with a P value of 0.003**.** ***Conclusion****:* The level of CRP was higher among patients with Coronary Artery Disease, than those with Normal Coronary Angiography. The level was higher among.

Keywords: Coronary artery disease, High sensitivity C-reactive protein, inflammation.

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INTRODUCTION

Cardiovascular disease (CVD) is a major cause of morbidity and mortality and ischemic heart disease (IHD) is one of its most common manifestations [1, 2].

Despite important advances in the diagnosis and treatment of coronary artery disease, it is still among the most common causes of death and disability in the world, which endangers global health.

While significant improvements have been made in prevention, diagnosis, and management, patients with IHD still have a high residual risk of cardiovascular (CV) events [1-4].

Multiple inflammatory markers such as C-reactive protein (CRP) have been associated with cardiovascular events [5, 6]. CRP is associated with CAD, ischemic stroke, and mortality by vascular and nonvascular causes [5, 7].

Knowing the risk factors for coronary disease such as hypertension, diabetes, insulin resistance, dyslipidemia, positive family history, smoking, limited movement, obesity, psychological stress, and recently homocysteine and inflammatory markers are of great importance [8, 9]. Factors such as age, diabetes, lipid profile, smoking, gender and heredity are introduced as risk factors for coronary artery disease [10, 11]. In recent decades, the inflammatory idea of atherosclerosis has been strongly suggested and hence the measurement of inflammatory markers' levels to determine the risk of cardiovascular events in patients with stable and unstable angina [12-21]. Inflammation has long been recognized as being closely related to CVD and specifically to the atherosclerotic process [22-24].

In recent decades substantial advances have been made in our understanding of the complex and multidimensional interplay between inflammation and IHD [22, 25-27] which led to the publication of several landmark clinical trials such as JUPITER, CANTOS, COLCOT and LoDoCo2, among others [28, 29-33].

One of these markers is High Sensitivity CRP (C-reactive protein) that has been indicated to increase in patients with coronary artery atherosclerosis and is associated with disease severity and its complications [34].

Underlying mechanisms of High sensitivity -CRP as a catalyst or intensifier of acute coronary syndrome, like MI, is not exactly known. Some researchers have shown that High sensitivity -CRP probably activate complement and cause continuing of the inflammation process of atheromatous plaques or create rupture or bleeding in the plaque, and whether CRP level is correlated with the severity of the injury remains unknown [35].

There are supporting association between inflammation and CVD, the concept that inflammation could be considered a risk marker or risk factor has continued to evolve in recent years. There is ample evidence supporting the role of inflammation at different stages of atherosclerosis, interacting with other factors to promote damage signaling and thus modulate this process [36-38]. It should be borne in mind that inflammatory stimuli can be associated with several CV risk factors, leading to atherogenesis and thus IHD [36, 39, 40].

Another factor that further influences disease expression is the intense interplay between inflammation and hemostasis, which can lead to a prothrombotic state [37, 41].

As amount of High sensitivity -CRP increases after many conditions, in myocardial infarction, measuring High sensitivity -CRP test can be one of the best and most sensitive laboratory tests that can predict signs of necrosis or inflammation of the cardiac muscle tissue. High sensitivity-CRP could cause bacterial opsonization.

Applications for diagnosis or measurement of High sensitivity-CRP in serum

1. Proving the existence of High sensitivity -CRP in serum is diagnostic for diseases such as infections, cancers, inflammatory diseases, especially heart attacks.
2. Measurement of serum High sensitivity -CRP or its serum titration can show the extent of disease.
3. Measurement of High sensitivity -CRP at different time intervals can control the disease treatment procedure, and effectiveness of the treatment. Given the importance of coronary artery disease as the leading cause of death in today's world, finding new methods and replacing early diagnostic facilities instead of treatment facilities and prevention of morbidity and mortality is very important. Therefore, with regard to uncertainties, we decided to assess the role of High sensitivity -CRP in coronary artery disease and the relationship between serum High sensitivity -CRP levels with the severity of coronary artery lesions.

The main objective of this study was to determine the relationship between serum levels of High sensitivity -CRP and Ischemic heart disease, among control and case groups, evaluating the association of the serum CRP levels according to gender, presence of diabetes, hypertension, lipid profile, and smoking and correlating it among case and control groups.

PATIENTS AND METHODS

This was a case-control study was conducted on a total of 404 patients, who attended to the Catheterization unit of Surgical Specialty Hospital-Cardiac Center/ Erbil City-Iraq. Patients from both genders, aged more than 30 were included in our study. The study timeline was from 1 of September 2021 to 1 of January 2022 at SSH/Cardiac Center. The patients of our study were grouped into two categories:

A. CAD patients (group I): Two Hundred and forty patients with coronary artery disease (CAD), and were diagnosed with CAD according to their Coronary angiography, and were regarded as obstructive CAD.
B. Healthy controls (group II): hundred and sixty-four selected subjects served as controls, all were healthy volunteers and had no evidence of any other disease based on their Normal Coronary Angiography.

Blood samples were collected from 240 CAD patients and 164 healthy controls. The collected samples were centrifuged at (3500 rpm) for 10 minutes. The separated serums were used for the measurement of CRP, S. total cholesterol, S.HDL, S.LDL, S. VLDL and S.TG and Cardiac Markers (serum troponin T Highly Sensitive, S.CK-MB).

The data was collected through a structured direct interviewer-administered questionnaire that is pretested with modifications made before its use in the study. The questionaries' 'includes the demographic variables (name, age, gender, and home address, time and date), clinical risk factors of the patient, family history, smoking habitual of the patients.

Exclusion criteria included history of acute coronary syndrome within 1 months prior to enrollment, History of Malignant condition (being under treatment and/or diagnosed with malignancies), chronic kidney disease—stage 3 or higher (baseline estimated

glomerular filtration rate < 60 mL/min/1.73 m^2), uncontrolled thyroid dysfunction, liver dysfunction (including viral hepatitis, cholestasis jaundice with bilirubin concentration > 1.5 mg/dl and/or alkaline phosphatase at least twice the upper limit of normal), calcium metabolic disorders, hormone replacement therapy, coexisting autoimmune disorders, acute infectious disease, chronic inflammatory disease, uncontrolled diabetes mellitus, ischemic or hemorrhagic stroke during 6 months before admission, glucocorticoids and/or androgens therapy, and lack of patient consent to participate.

Data from the measurement of biochemical lab results with angiographic information and risk factors were logged in the checklist, previously designed for this purpose, and results were analyzed by SPSS software and analyzed by Pearson correlation test, t-test, and Chi test.

All works were performed in accordance with the Declaration of Helsinki; verbally Informed consent has been taken from each patient. Complete explanation of the nature and aim of the study has been given to each participant, and reassure about confidentiality of the data and their anonymity. They were also given the option of withdrawal from the study whenever wanted.

RESULTS

404 patients1 were evaluated for this study. 57.4% of them were CAD cases and 42.6% were controls.

Demographic characteristics

The mean age was 55.9 ±10.6, ranging from 30 to 77 years of age. Most of the patients (31.7%) were in the 60-69 age group, followed closely by the 50-59 age group (29.2%), 40-49 age group (24.3%), >70 age group (10.9%) and the <39 age group (4%). The majority of the study population (58.4%) were males and (41.6%) were females.

The largest part of the patients was overweight (37.6%) and obese class 1 (37.1%), followed by normal weight (14.9%), obese class 2 (7.4%), underweight (5%) and obese class 3 (2.5%).

Concerning their smoking status, the majority (67.8%) were non-smokers and (16.3%) were ex-smokers. And (15.9%) were smokers. Regarding life style of participants, 46.5% reported to have stressful lives while 53.5% reported relatively Non-stressful lives. This is summarized in Table 1.

Table-1: Sociodemographic characteristics of the sample population

Characteristics	Frequency (n)	Proportions (%)
Age (in years)		
• <39	16	4
• 40-49	98	24.3
• 50-59	118	29.2
• 60-69	128	31.7
• >70	44	10.9
Gender		
• Male	236	58.4
• Female	168	41.6
BMI		
• Underweight	2	5
• Normal weight	60	14.9
• Overweight	152	37.6
• Obese class 1	150	37.1
• Obese class 2	30	7.4
• Obese class 3	10	2.5
Smoking Status		
• Non-Smoker	274	67.8
• Ex-Smoker	66	16.3
• Smoker	64	15.9
Stressful Life		
• Yes	188	46.5
• No	216	53.5

In regards to the past medical history of the study population, 48.5% had hypertension 49.5% of the patients had a family history of CAD, Half of the patients had IHD. 34.2% of the patients had diabetes mellitus. 38.1% had dysregulated lipid profile. Only28.2% of the patients had had a previous PCI. In regard of COVID-19, 49% of the population had had a previous Covid-19 infection while 51% had not. This is summarized in Table 2.

Table-2: Past medical history of the study population

Past Medical History	Frequency (n)	Proportions (%)
Hypertension		
• Yes	196	48.5
• No	208	51.5
Family History		
• Yes	200	49.5
• No	204	50.5
Ischemic Heart Disease		
• Yes	202	50
• No	202	50
Diabetes Mellitus		
• Yes	138	34.2
• No	266	65.8
Hyperlipidemia		
• Yes	154	38.1
• No	250	61.9
Previous PCI		
• Yes	114	28.2
• No	295	71.8
Previous Covid-19 Infection		
• Yes	198	49
• No	206	51

The mean of CRP level amongst cases was higher (6.2 ± 10) than the controls (3.5 ± 4.7), and this was significant with a $P = 0.022$.

In our study we found that Highly Sensitive-CRP was high amongst Case Group (Patients with CAD) by 70% while comparing to only 30% of Control group who had High CRP levels. And this was Statistically significant with a P value of 0.003. This is shown in Figure1.

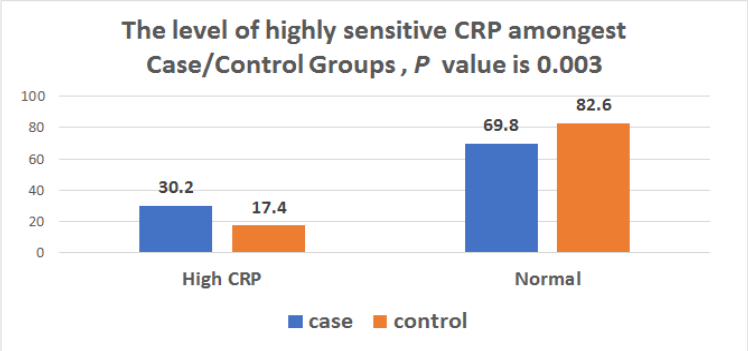

Fig-1: The level of highly sensitive CRP among both groups

We found that amongst the case group (Patients with CAD) the frequency of higher levels of CRP was noticed to be amongst female gender (39.4%) than comparing it to male gender (26.5%) and this was statistically significant with a P value of 0.05, this is summarized in Figure 2.

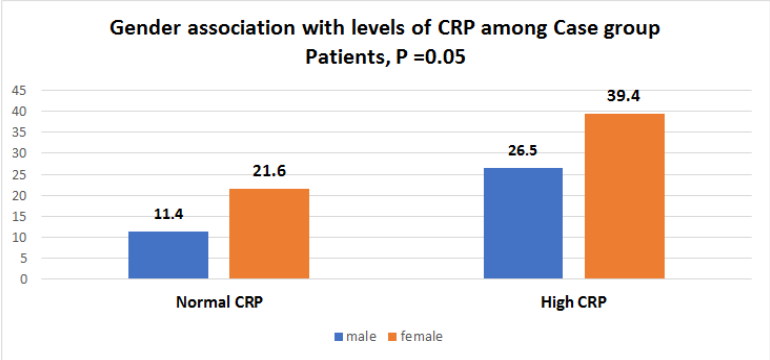

Fig-2: Association of gender with High levels of CRP.

Regarding the Lipid Profile of the Patients, there was a significant difference between the mean level of cholesterol among the cases and controls. Surprisingly, the controls had a higher cholesterol level (150 ± 39) compared to the cases (122 ± 34). This was significant with a P value of <0.001. The controls had higher HDL levels (35.4 ± 8.5) compared to the cases (31.7 ± 7.7). This was also significant, P = 0.002. The mean triglyceride level was found to be higher among the controls (165.5 ± 79.5) rather than the cases (149.3 ± 85.2). This was not significant. P = 0.17.

Chest pain was experienced by 88.8% of the cases and 23.3% of the controls. Dyspnea was seen in 65.5% of the cases and 11.6% of the controls. 54.3% of the cases had palpitation as well as 14% of the controls. 80.2% of the cases had shoulder/back pain while 29.1% of the controls had it. Sweating was seen in 56% of the cases and 18.6% of the controls. Only 26.7% of the cases experienced nausea and vomiting and 4.7% of the controls. Regarding atypical presentations, 1.7% of the cases and 2.3% of the controls had it. This is summarized in figure 3.

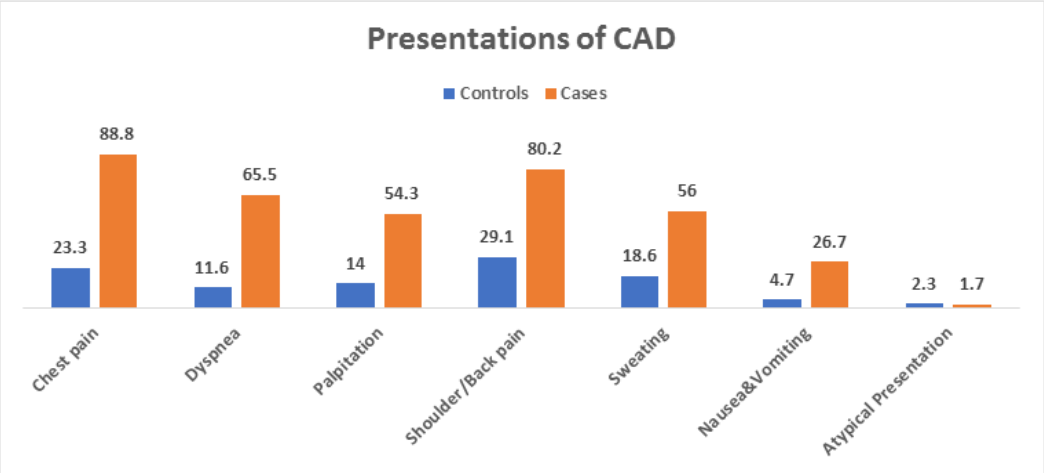

Fig-3: CAD presentations in the study population

Based on the Angiographic profile of the patients, those who were considered to have CAD, and had had high levels of CRP were about 60%, and 46.7% of patients with CAD had had normal CRP levels. Those of Normal Coronary angiography, only 40% had high levels of CRP and the remaining line into normal level of CRP. And this was statistically significant with P value of 0.05. This is all summarized in Figure 4.

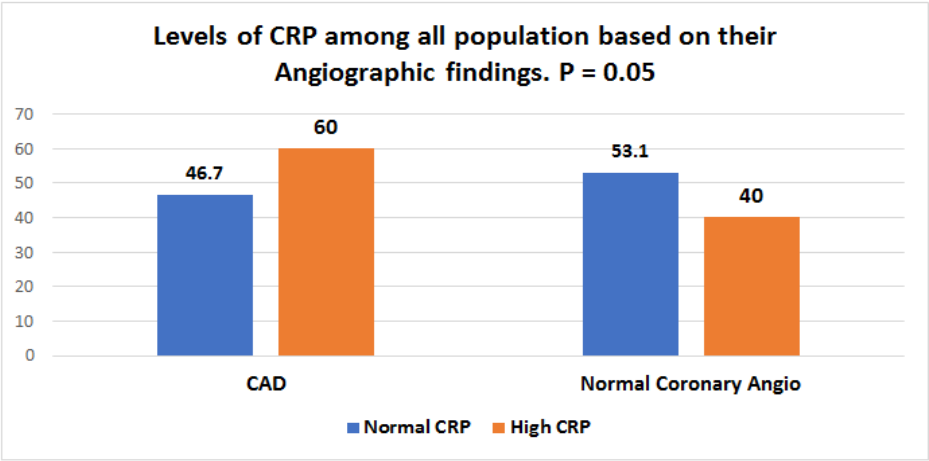

Fig-4: levels of CRP among patient with CAD and Normal Coronary Angiography based on their Angiographic Profile.

There was a significant association seen between certain presentations and age groups. The highest rate of dyspnea was seen among the 50-59 and the 60-69 age groups (34.2%) each. Followed by the >70 age group (19.7%) and the 40-49 age group (11.8%). 0% among the <39. This was significant with a P value of 0.048.

Among the cases, the highest percentage of sweating (30.8%) was seen in the 50-59 age group. Followed by the 40-49 (26.2%) and the 60-69 (24.6%) age groups, respectively. 18.5% of sweating was seen in the >70 age group. And 0% among the <39. This was significant with a P value of 0.006. This is summarized in Table 3.

Table-3: Dyspnea and sweating with age groups

Presentation among cases of CAD.	<39	40-49	50-59	60-69	>70	P value
Dyspnea						0.048
• Yes	0%	11.8%	34.2%	34.2%	19.7%	
• No	2.5%	27.5%	22.5%	40%	7.5%	
Sweating:						0.006
• Yes	0%	26.2%	30.8%	24.6%	18.5%	
• No	2%	5.9%	24.9%	51%	11.8%	

Table-4: The mean of Control/Case Group for each variable of Biochemical Profile

Lab Results	Mean ± SD	P value
Cholesterol		<0.001
• Cases	122 ± 34	
• Controls	150 ± 39	
HDL		0.002
• Cases	31.7 ± 7.7	
• Controls	35.4 ± 8.5	
LDL		<0.001
• Cases	57.7 ± 21.4	
• Controls	80.5 ± 31.1	
VLDL		0.05
• Cases	29.4 ± 17.6	
• Controls	35 ± 22.5	
Triglycerides		0.17
• Cases	149.3 ± 85.2	
• Controls	165.5 ± 79.5	
Troponin		0.001
• Cases	60.3 ± 151.5	
• Controls	7.4 ± 5	
CK-MB		0.243
• Cases	13.8 ± 10.8	
• Controls	12.3 ± 5.6	
Vitamin D		0.55
• Cases	21.8 ± 12.3	
• Controls	22.9 ± 13.8	
GGT		0.144
• Cases	36.1 ± 32.5	
• Controls	29.8 ± 26.5	
CRP		0.022
• Cases	6.2 ± 10	
• Controls	3.5 ± 4.7	

Regarding the Biochemical profile of case and control groups, we compared the mean of both population and it's all summarized in Table 4 with P values.

When categorizing BMI of all participants, we found that the higher CRP levels were found among those of Class III-Obese Patients, in which 60% of all Obese-Class III patients had had highest levels of CRP, comparing to all other groups, this was statistically significant with P value of 0.028. Figure 5 summarizes all the details.

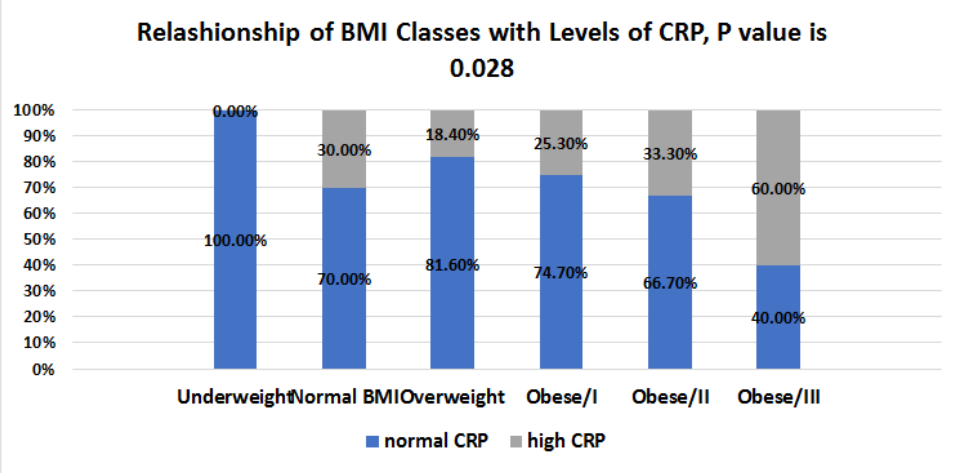

Fig-5: Levels of CRP among different BMI categorized Groups

DISCUSSION

In summary, the objective of this study was to identify CRP as an inflammatory marker in estimating coronary artery disease in patients with Coronary Artery Disease and a Control group pf Normal Coronary Angiography.

In the light of our results we found that level of CRP was higher among patients with CAD- based on their Coronary Angiography finding, this was parallel in finding of Berk and Liuzzo have found that serum levels of CRP increased in patients with stable and unstable angina and this marker is considered as a reliable indicator to predicting future events in these patients [42, 43]. These studies also found that about 13% of patients with CAD had increased serum CRP levels. This level was much higher in our study in which 30.2% of all the patients in case group of CADs had had a high level of CRP level.

A meta-analysis that merged the results of seven major studies clearly indicated that even after the correction of a number of important factors in coronary artery disease, CRP still remained a risk factor in the final analysis [44].

Ford and colleagues conducted a study to examine the association between risk factors for cardiovascular diseases and found a significant relationship between serum levels of CRP and other risk factors such as age, BMI, and serum total cholesterol level [45]. This was parallel with our findings, in which cholesterol level was much higher among case groups.

In our study we found that patients with High CRP, 23.5% of the patient in case group had had high CRP, while the frequency was much lower among control group patients. Regarding DM as a risk factor for CAD, 27.5% of DM patients had high levels or CRP. Another study also confirmed similar relationship between serum CRP levels, smoking, and diabetes [46]. The CRP levels in association with different gender, was found to be more among female gender, Ridker and colleagues in Another prospective study conducted similar results, which they found that the measurement of serum CRP predicts the risk of future cardiovascular events in women [47].

Obesity is the major factor associated with elevated CRP in individuals with the metabolic syndrome. CRP levels in the range suggesting a source of inflammation are more common among obese subjects than in no obese subjects [48]. This was parallel in our study in which we also found association of High CRP levels, the higher the BMI the higher the mean of the CRP of the population.

CONCLUSION

There is role of inflammation in the development and fate of an atherosclerotic plaque and consequence of Coronary Artery Disease. CRP as one of the main inflammatory markers can be evaluated.

Considering the potential risk of coronary inflammatory process as a new variable, it can help discover new cases of coronary lesions and follow-up and control of the selected cases.

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