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Original Article

Inflammatory indices IL-6, TNF-α, CRP, and hs-CRP in candidates for coronary artery bypass graft surgery

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ABSTRACT

Objectives: The elevation of inflammatory factors, such as tumor necrosis factor α (TNF-α) and high-sensitivity C-reactive protein (hs-CRP), is associated with a high risk of coronary artery disease (CAD). The primary objective of the present study was to identify the primary inflammatory factors in patients who were candidates for coronary artery bypass graft (CABG).

Methods: This study included 30 subjects scheduled to undergo CABG surgery, as well as 30 control subjects. Serum levels of hs-CRP, interleukin 6 (IL-6), and TNF-α were analyzed using enzyme-linked immunosorbent assay (ELISA) kits.

Results: There were no significant differences in body mass index (BMI) and age between the patient and control groups. However, the patient group had significantly higher triglyceride (TG) levels compared to the control group ($P < 0.05$). Additionally, the patient group exhibited significantly elevated levels of inflammatory cytokines IL-6 and TNF-α ($P < 0.001$ for both), as well as higher circulating levels of CRP and hs-CRP compared to the control group.

Conclusion: The findings of the present study indicated that patients recommended for surgical intervention often have elevated levels of inflammatory factors. It is advisable to take these findings into consideration before proceeding with surgery.

Keywords: Coronary Artery Bypass Graft; CRP; hs-CRP; IL-6; TNF-α

Abbreviations: BMI: body mass index; CABG: coronary artery bypass graft; CAD: coronary artery disease; ELISA: enzyme-linked immunosorbent assay; FBS: fasting blood sugar; hs-CRP: high-sensitivity C-reactive protein; ICAM-1: intercellular adhesion molecule 1; IL-6: interleukin 6; MCP-1: monocyte chemoattractant protein 1; TNF-α: tumor necrosis factor α; TC: total cholesterol; TG; triglyceride; VCAM-1: vascular cell adhesion molecule 1.

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Introduction

Coronary artery disease (CAD), characterized by a reduction in blood flow to the heart muscle, occurs as a result of atherosclerotic plaque formation within the coronary arteries (1). This disease significantly contributes to both mortality and morbidity in the majority of countries, accounting for nearly 18.6 million CAD deaths worldwide in 2019 (2, 3). Mechanisms such as inflammation, cholesterol accumulation, and endothelial dysfunction are recognized as key events in the progression of CAD (3, 4). Inflammation triggers the initial stages of atherosclerosis, and an elevation in inflammatory cytokines correlates with an increased risk of cardiovascular diseases (CVDs) (5, 6). It has been shown that the mRNA expression of monocyte chemoattractant protein 1 (MCP-1), intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), tumor necrosis factor α (TNF-α), and interleukin 6 (IL-6) are elevated in the serum of patients with coronary heart disease (7). Furthermore, the circulation levels of these molecules are correlated with an increased risk of the disease (8). Additionally, research has demonstrated that C-reactive protein (CRP), IL-6, and ICAM-1 are linked to progressive changes in atherosclerosis over a 12-year period (9, 10). As a result, these circulating inflammatory markers can be considered predictive indicators for the progression of peripheral atherosclerosis.

Cell adhesion molecules, including VCAM-1, ICAM-1, and certain selectins, facilitate the binding of inflammatory cells, such as monocytes, to sites where early plaque formation begins. These infiltrating monocytes subsequently transition into resident macrophages within the sub-endothelial space (11, 12). Activated macrophages secrete pro-inflammatory cytokines into atherosclerotic plaques, leading to the apoptosis of vascular smooth muscle cells and the release of matrix vesicles enriched with elevated levels of calcium and phosphate (13). These vesicles initiate the process of calcium deposition, thus contributing to the development of plaques (14). It is important to highlight that calcium deposition stimulates more inflammatory responses, thereby establishing a detrimental cycle in which inflammation and calcification mutually reinforce each other. This cycle, in turn, leads to the exacerbation of the condition and the further growth of plaques (14).

The main therapeutic approaches for patients with CAD involve a combination of lifestyle adjustments, including dietary modifications and exercise, along with medical interventions. When primary treatments prove ineffective and symptoms continue to persist and worsen, cardiac bypass surgery is typically recommended to enhance blood supply to the heart (14). The process involves isolating a blood vessel from the chest, arms, or legs and employing this vessel to create a bypass around the obstruction in the coronary artery that supplies the heart. Considering the close interconnection between inflammatory markers and CAD, the primary objective of this study was to examine the levels of inflammatory markers in patients who were candidates for cardiac bypass surgery in comparison to a control group.

Materials and methods

The research was conducted in accordance with the principles outlined in the Declaration of Helsinki and received approval from the Ethics Committee of Kerman University of Medical Sciences in Kerman, Iran (Approval ID: IR.KMU.AH.REC.1399.131.). The study included 30 subjects scheduled to undergo coronary artery bypass graft (CABG) surgery, as well as 30 control subjects. The inclusion criteria were having a body mass index (BMI) lower than 30 kg/m², abstaining from alcohol consumption, and being a candidate for CABG surgery as determined by a specialist. The exclusion criteria consisted of a history of liver diseases and cancer, a history of cardiac events, the use of medicinal supplements, and patient unwillingness to continue participating in the study. All participants signed written informed consent. For this study, 30 patients diagnosed with CAD were selected from those referred to Shafa Hospital in Kerman. Subsequently, blood samples were collected from those who met the entry criteria prior to surgery. The control group included those with no history of CVDs. Individuals who smoked or consumed alcohol were excluded from the study.

To conduct the experiments, blood samples (5 mL) were collected from each participant after a fasting period of 12 h. The samples were used to assess various parameters, including fasting blood sugar (FBS) and inflammatory markers, as well as triglyceride (TG) and cholesterol levels.

Anthropometrics and biochemical measurements

Anthropometric measurements were documented for each individual participating in the study. BMI was calculated by dividing weight by the square of height. After a 10-h overnight fast, 4 mL of venous blood was collected from each participant. The collected serum samples underwent immediate centrifugation (at 1000× g for 15 min), and then were divided into smaller aliquots and stored at a temperature of -70˚C. Biochemical markers, including total cholesterol (TC), triglycerides (TG), and fasting blood glucose (FBG) were assessed using the relevant kits.

Measurement of inflammatory indicators

Serum samples were analyzed for levels of CRP, hs-CRP, IL-6, and TNF-α using enzyme-linked immunosorbent assay (ELISA) kits (Karmania Pars Gene, Kerman, Iran)

in accordance with the manufacturer's instructions (15). The minimum detectable concentrations were 3 pg/mL for IL-6, 2 pg/mL for TNF-α, and 10 ng/mL for hs-CRP. Intra-assay and inter-assay coefficients of variation (CVs) were 3% and 9% for IL-6, 3% and 8% for TNF-α, and 10% and 12% for hs-CRP, respectively. Absorbance readings were obtained at 450 nm using an ELISA reader (BioTek, Winooski, Vermont, USA).

Statistical analyses

Statistical analyses were performed using SPSS 22 software (SPSS, Chicago, IL, USA). Initially, the normal distribution of variables was assessed using the Kolmogorov-Smirnov test. Statistical comparisons between the two groups were conducted using Student's t-test for variables exhibiting a normal distribution and the Mann-Whitney test for variables displaying a non-normal distribution. The occurrence of diabetes mellitus and hypertension in patients was assessed via comparison to control individuals, employing the $\chi 2$ test.

Results

Table 1 displays the clinical characteristics of the study participants. As observed, there were no notable differences in terms of BMI and age between the groups ($P > 0.05$).

Regarding the parameters of kidney function, no significant difference was observed in the circulation levels of urea and creatinine between the patient group and the control group. Moreover, the lipid profile revealed considerably elevated TG concentrations within the patient group with a significance level of $P < 0.001$ as opposed to the control group. The TC level did not exhibit any difference between the two groups.

Serum levels of TNF-α, IL-6, CRP, and hs-CRP

As depicted in Figure 1, it is observed that the inflammatory cytokines IL-6 and TNF-α are notably higher in the patient group compared to the control group ($P < 0.001$ for both). Similarly, it is found that the circulating levels of CRP and hs-CRP are significantly higher in the patient group than in the control group ($P < 0.001$ for both).

Evaluating the occurrence of diabetes and high blood pressure in the patient and control groups

Out of the 30 patients participating in the study, it is observed that 13 exhibit high blood pressure. In the control group, 12 individuals are found to have high blood pressure. In terms of the occurrence of diabetes, the results appear to be similar to those regarding high blood pressure, with 13 individuals in the patient group and 9 individuals in the control group suffering from diabetes. Consequently, it is concluded that there are no statistically significant differences between the two study groups with respect to blood pressure and diabetes.

Correlation of serum hs-CRP with the studied parameters

Correlations between hs-CRP levels and the biochemical parameters and measured clinical variables in the studied population are shown in Table 3. It is indicated that circulating levels of hs-CRP positively correlate with the levels of glucose ($r = 0.314$, $P = 0.017$), IL-6 ($r = 0.719$, $P < 0.001$), and TNF-α ($r = 0.493$, $P < 0.001$).

Table 1: Clinical characteristics of the study population.

Variables	Control (n = 30)	Patient (n = 30)	P-value
Gender (sex) w/m	15/15	11/19	
Age (years)	57.3667 ± 1.23221	60.4667 ± 1.01905	0.057
BMI (kg/m^2)	25.7781 ± 4.62895	26.1500 ± 2.69897	0.706
FBG (mg/dL)	116.8148 ± 15.38166	133.2167 ± 10.29272	0.024
Urea (mg/dL)	28.2222 ± 7.65272	25.0067 ± 5.43779	0.077
CR (mg/dL)	0.9377 ± 0.03161	0.8819 ± 0.07739	0.089
TG (mg/dL)	99.3567 ± 7.54373	142.8233 ± 7.76481	< 0.001
TC (mg/dL)	147.8103 ± 5.77052	155.0500 ± 7.72376	0.43

BMI: Body mass index; FBG: Fasting blood glucose; CR: Creatinine; TG: Triglyceride; TC: Total cholesterol

Table 2: Comparing the patient and control groups in terms of the occurrence of diabetes and high blood pressure.

Variables	Cardiovascular disease status		Total	P-value
	No	Yes		
High blood pressure				0.793
No	18	17	35	
Yes	12	13	25	
Diabetes				0.284
No	21	17	38	
Yes	9	13	22	

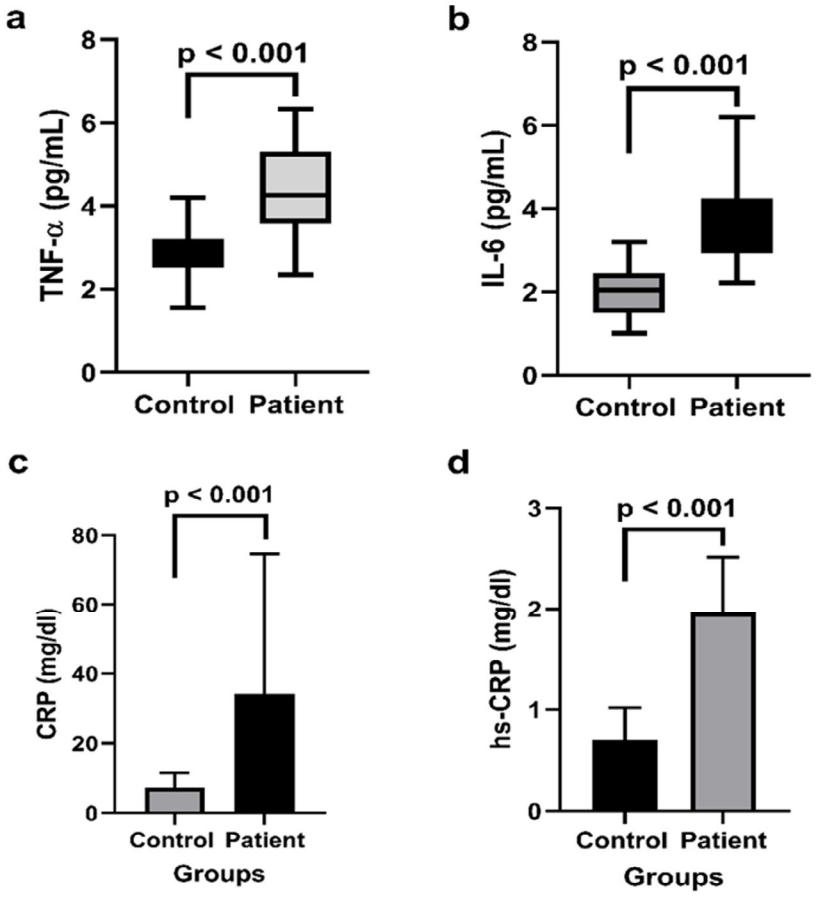

Figure 1: The serum levels of inflammatory indicators in the patient group.
Comparisons were made using Student's t-test and the Mann-Whitney test for variables exhibiting normal and non-normal distributions, respectively.

Table 3: Association between hs-CRP and different clinical variables

	BMI	Blood pressure	FBG	Urea	CR	TG	TC	IL-6 (pg/mL)	TNF-α (pg/mL)
Correlation coefficient	0.122	0.100	0.314	-0.105	-0.237	-0.372	0.090	0.719	0.493
P-value	0.355	0.449	0.017	0.436	0.068	0.003	0.496	< 0.001	< 0.001

FBG: Fasting blood glucose; CR: Creatinine; BP: Blood pressure; TG: Triglyceride; TC: Total cholesterol

In addition, a negative correlation is observed between hs-CRP and TG levels (r = - 0.372, P = 0.003).

Discussion

CABG is a surgical technique used to bypass obstructed coronary arteries in order to restore regular blood circulation to the heart muscle. This procedure is often referred to as a "heart bypass". Emergency CABG may be necessary in cases of myocardial infarction, accidental findings during angiography, shock, continuous ischemia, and similar conditions (16). This study investigates the circulation levels of inflammatory markers in patients who are candidates for CABG. The results reveal that inflammatory indicators, including CRP, hs-CRP, IL-6, and TNF-α, exhibit significant elevations in the patient group.

Obesity, as identified by a BMI > 30 kg/m2, is a well-established factor associated with an increased risk of both coronary heart disease and metabolic disorders (17-20). Nevertheless, in individuals diagnosed with diabetes, an elevated BMI does not appear to be a significant independent risk factor for cardiac events (21) and is not associated with the score of coronary artery calcium and the presence of coronary plaques (22). Similarly, the present study finds no association between CAD and BMI. The discrepancies in findings across different studies could be attributed to variations

in the studied patient populations, including differences in race, disease stage, and other conditions associated with the disease, such as diabetes.

Studies have demonstrated that high blood pressure is a significant risk factor for heart failure, coronary heart disease, and stroke (23). The risks of both cardiovascular and expanded cardiovascular mortality are minimized when systolic blood pressure ranges from 120 to 129 mm Hg. However, these risks are substantially increased when systolic blood pressure is ≥ 160 mm Hg or when diastolic blood pressure is ≥ 90 mm Hg (24). Nonetheless, in the present study, the patient group does not show a significant difference compared to the control group in terms of blood pressure. It is important to note that patients who participate in this study are on medication during the analyses. Consequently, the results may have been influenced by the use of drugs and may not accurately reflect the true condition of the disease.

Overall, serum TG, TC, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) levels, as well as the TC/HDL-C and LDL-C/HDL-C ratios are independent predictors of CVD risk (25, 26). In the present study, cholesterol levels in the patients show no significant differences. However, the average TG level in the patient group is 142.8 mg/dL, which falls within the borderline range and is higher than that in the control group. One limitation of this study is the lack of HDL and LDL measurement. Therefore, a definitive assessment of the role of dyslipidemia in the pathogenesis of the disease cannot be made based on the results of this study.

Inflammation is now widely recognized as the common underlying mechanism responsible for the primary complications associated with atherosclerosis, ischemic heart disease, and stroke (27-30). This study reveals that inflammatory markers, namely IL-6, TNF-α, CRP, and hs-CRP, exhibit elevated levels in patients who are candidates for CABG surgery. Moreover, the elevated risk of recurrent coronary events following a myocardial infarction is primarily observed in individuals with the highest levels of TNF-α (31). Moreover, it is found that IL-6, as an indicator of systemic inflammation, may be linked to the clinical progression of CVD in elderly patients (13, 32). CRP and its more sensitive counterpart, hs-CRP, have been utilized to predict the risk of coronary heart disease. A study demonstrates that participants with an hs-CRP level equal to or greater than 1.08 mg/L are at a higher risk of developing coronary heart disease than those with an hs-CRP level below 1.08 mg/L (33). Increased levels of serum hs-CRP are strongly correlated with the angiographic severity of CAD (34). In the present study, there is a direct correlation between serum levels of hs-CRP and the parameters of inflammation, such as IL-6 and TNF-α. The results are consistent with those of previous studies that have investigated the relationship between hs-CRP and other inflammatory markers under similar conditions (35, 36). hs-CRP also displays a positive correlation with FBG. Similarly, a study conducted on groups of healthy postmenopausal women demonstrates a direct increase in FBG levels as hs-CRP levels rise (37). It is also revealed that when individuals are grouped based on blood glucose levels, hs-CRP shows an increasing trend, indicating that rising glucose levels are associated with increasing hs-CRP levels (38). These findings suggest that hs-CRP may play a role in regulating metabolic pathways in addition to its role in inflammation.

Conclusion

The results of the present study indicate that patients who are candidates for GABC surgery display significantly higher levels of inflammation, as evidenced by elevated levels of inflammatory cytokines IL-6, TNF-α, CRP, and hs-CRP when compared to the control group. Therefore, it is important to take this finding into consideration before proceeding with surgery.

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Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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