

Estimation of interferon gamma and some inflammatory atherogenic biomarkers levels in obese coronary atherosclerotic patients

Received: 24/1/2019

Accepted: 13/5/2019

Alia Talat Abdulrahman^{1*}

Ruqaya Muhammed Gharib Taher AL-Barzinji²

Abstract

Background and objective: Coronary atherosclerosis is an inflammatory disease that may be caused by numerous factors. One of the most important factors is obesity; there are high concentrations of interferon gamma (IFN- γ) in obese patients. This study aimed to assess the levels of proinflammatory markers IFN- γ and high sensitive C- reactive protein (Hs-CRP) in obese coronary atherosclerotic patients and determine its correlation with lipid profiles.

Methods: The present case-control study was carried out between December 2017 and May 2018 in the Cardiac Center-Surgical Specialty Hospital in Erbil city. It included 49 coronary atherosclerotic patients, 25 males and 24 females, and 39 controls. The sera were subjected to estimate of some inflammatory biomarkers including IFN- γ , Hs-CRP, and lipid profile such as total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoproteins cholesterol (LDL-C) and very low- density lipoproteins (VLDL-C).

Results: Serum concentrations of IFN- γ and Hs-CRP in coronary atherosclerotic patients were increased significantly than controls ($P = 0.031$, $P = 0.001$), respectively. Indeed the same above results were seen in obese coronary atherosclerotic patients and controls than non-obese coronary atherosclerotic patients controls. The mean concentration of lipid profile in obese coronary atherosclerotic patients was decreased than non -obese coronary atherosclerotic patients and controls, with no significant differences ($P \geq 0.05$). There was a weak negative significant correlation between IFN- γ and HDL-C in obese coronary atherosclerotic patients ($r = -0.456$; $P = 0.040$).

Conclusion: Proinflammatory cytokine as IFN- γ played a vital role in the pathophysiology of obese atherosclerotic patients in combination with Hs-CRP and LDL-C, which could be used as predictors for progressive the disease.

Keywords: Coronary atherosclerosis; Obesity; Proinflammatory marker; Interferon gamma.

Introduction

Atherosclerosis, an underlying cause of cardiovascular disease, is responsible for around half of all deaths in the wide world.¹ Interferon gamma (IFN- γ) is a signature cytokine of Th1 cells that play a key role in the atherosclerosis process.² It has atheroma-promoting properties, and involved both in early and late stages of atherosclerosis by promoting the recruitment and activation of T cells and macrophages, leads to the production

of proinflammatory cytokines.³ Several immunohistochemical studies have discovered localization of IFN- γ in the atherosclerotic lesion.⁴ Studies also report that the removal of IFN- γ or its receptors leads to a reduction in atherosclerosis.⁵ Obesity is one of the vital risk factors for atherosclerosis and cardiometabolic syndrome. There is evidence that proinflammatory cytokine, including IFN- γ are overexpressed from adipose tissue. Various mechanisms have been suggested

¹ Department of Anesthesia, Erbil Medical Technical Institute, Erbil Polytechnic University, Erbil, Iraq.

² Department of microbiology, College of Medicine, Hawler Medical University, Erbil, Iraq.

* Correspondence: Alia_talat_bio@yahoo.com

to link obesity to atherosclerosis. Inflammation by obesity has been associated with the activation of adipose tissue macrophages, T cells, and B cells,⁶ and reflected by increased CRP levels, systemic oxidative stress, and elevation of circulating levels of chemokines, and various proinflammatory cytokines mainly IFN- γ .^{7,8} Furthermore, an elevated level of LDL oxidized by reactive oxygen species (ROS) and modified to oxidized LDL (OxLDL), which is thought to be the primary initiating event in atherosclerosis by secretion of IFN- γ .⁹ There was limited data available in our region regarding proinflammatory cytokines especially IFN- γ as risk factors in obese coronary atherosclerosis disease. The current study aimed to assess the levels of proinflammatory markers IFN- γ and Hs-CRP in obese coronary atherosclerotic patients and to find out its correlation with lipid profiles.

Methods

The present case-control study was performed between December 2017 to May 2018, included 49 patients with coronary atherosclerosis (CAPs); 25 males and 24 females. Their age ranged between 43-78 years. Also, 39 individuals were selected as control (19 males and 20 females) with normal coronary angiography, who had no history of clinical evidence of any acute or chronic inflammatory or autoimmune diseases. Their age ranged between (31-78) years. They were attending Cardiac Center-Surgical Specialty Hospital - in Erbil city. The subjects of both the study and control groups were subgroups based on the WHO classification of body mass index (BMI).¹⁰ BMI was calculated for all individuals by the formula, $BMI = \text{Weight} / \text{Height (m)}^2$, then classified according to BMI into three groups: BMI <25 represented the normal weight, BMI 25-29 represented the overweight, and BMI >30 represented the obese. All patients underwent percutaneous coronary intervention (PCI) as having >40% stenosis

of one major coronary artery. Patients with acute coronary syndrome were excluded from this study. All participants were subjected to personal interview through specially designed questionnaires format. Verbal consents were taken from all participants before participation in the current study. The Ethics Committee of Medical Research at the College of Medicine, Hawler Medical University approved the study protocol. All procedures were in accordance with the established ethical standards. A total of 10 mL of venous blood was collected in a disposable syringe from all the subjects following standard precautionary measures. Collected blood samples were allowed to stand at room temperature for 30 minutes and then centrifuged at 3000 rpm for 15 minutes to obtain serum, which was stored at $-80\text{ }^{\circ}\text{C}$ until further processing. Serum IFN- γ levels were measured with enzyme-linked immunosorbent assay (ELISA) kit using Human Interferon- γ (IFN- γ) provided by Thermo Fisher Scientific, USA, catalog # BMS228 / BMS228TEN, according to manufactures instructions; the standard range was 1.6pg/mL - 100pg/mL. Levels of Hs-CRP and lipid profile, including TC, TG, HDL-C, LDL-C, and VLDL-C were measured on the principle of the enzymatic colorimetric test using Cobas c111 (Roche Diagnostics, GmbH).

Statistical analysis

Data were statistically analyzed using the statistical package for the social sciences (version 19). The data were expressed as mean \pm standard error (SE) or with frequencies and percentages. Differences in mean values between groups were compared using independent sample student's t-test, ANOVA, and Duncan test. Chi-Square test (X^2) was used as a non-parametric test. The Pearson Correlation Coefficient test was used to detect the relationship between serum IFN- γ levels and other inflammatory atherogenic biomarkers. The difference was considered statistically significant if P was ≤ 0.05 .

Results

Table 1 shows the baseline characteristics of CAPs and controls. Patients with coronary atherosclerosis were significantly older than the control group ($P = 0.007$). There were no significant differences regarding to gender, body mass index, and family history of coronary artery disease ($P = 0.830$, $P = 0.190$, and $P = 0.082$, respectively). Whereas, there

were highly significant differences in statin users when compared CAPs with controls ($P = 0.001$). Proinflammatory cytokine IFN- γ and Hs-CRP were significantly higher in CAPs compared to control groups ($P = 0.031$ and 0.001 , respectively). The lipid profile within normal ranges with no significant differences between CAPs, and controls ($P \geq 0.05$).

Table1: The baseline characteristics between the CAPs and the control.

| Characteristics | CAPs No=49 | Control No=39 | P value |
|---------------------------------------|---------------|------------------|---------|
| Age(years) | 60.1±1.15 | 54.25±1.92 | 0.007** |
| Sex No (%) : | | | |
| Male | 25 (51.02) | 19 (48.72) | 0.830 |
| Female | 24 (48.48) | 20 (51.28) | |
| Family history of CAD: No% | 28 (57.1) | 15(38.4) | 0.082 |
| BMI | 28.4±0.63 | 27.0±0.82 | 0.190 |
| Obesity classification: No (%) | | | |
| Normal | 12 (24.4) | 15 (38.4) | |
| Overweight | 18 (36.7) | 15 (38.4) | 0.082 |
| Obese | 19 (38.7) | 9 (23.2) | |
| Inflammatory marker : | | | |
| IFN- γ (pg/mL) | 5.52±0.38 | 3.45±0.32 | 0.031* |
| Hs-CRP (mg/L) | 14.7±2.69 | 3.068±0.4 | 0.001** |
| Lipid profile: | | | |
| Total cholesterol(mg/dl) | 144.6±5.85 | 149.5±8.0 | 0.601 |
| Triglycerides(mg/dl) | 127.2±10.9 | 150±18.19 | 0.305 |
| HDL-Cholesterol (mg/dl) | 38.2±1.52 | 40.09±1.43 | 0.908 |
| LDL-Cholesterol (mg/dl) | 83.6±5.42 | 82.8±5.85 | 0.232 |
| VLDL-Cholesterol(mg/dl) | 30.0±2.45 | 31.1±3.67 | 0.106 |
| Statins No%: | 45 (91.8) | 9(23.0) | 0.001** |

Data are presented as number (%) and mean \pm standard error; IFN- γ : Interferon-gamma; Hs-CRP: High sensitive C - reactive protein; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; VLDL: Very Low Density Lipoprotein; * P values ≤ 0.05 is considered to be statistically significant; ** P value < 0.01 : Highly significant.

Table 2 has shown that serum concentration of proinflammatory marker IFN- γ and Hs-CRP levels elevated significantly and high significantly in obese CAPs and controls compared to non-obese CAPs and non-obese controls ($P = 0.012$; $P = 0.001$) respectively. The same mentioned result were revealed regarding pro-atherogenic lipid LDL cholesterol, while, in contrast, HDL-C was non-significantly changed ($P = 0.405$).

Table 3 shows that IFN- γ and Hs-CRP levels were elevated significantly in higher obesity subclass (obese ≥ 30) of CAPs compared to the control group ($P = 0.022$ and 0.013 , respectively). Regarding lipid profile, there was increased pro-atherogenic lipid LDL-C and decreased anti-atherogenic lipid HDL-C in overweight CAPs compared to obese subclass. However, the differences were not statistically significant changes ($P = 0.590$).

Table 2: A comparison of inflammatory and lipid profile markers between obese and non-obese CAPs and control.

| Parameters | CAPs | | Control | | P value F test |
|-----------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------|
| | Obese No=19 | Non-Obese No=30 | Obese No=9 | Non-Obese No=30 | |
| | Mean \pm SE | Mean \pm SE | Mean \pm SE | Mean \pm SE | |
| IFN- γ (pg/mL) | 6.52 \pm 0.79 ^a | 4.88 \pm 0.33 ^{bd} | 5.0 \pm 0.57 ^{ac} | 4.28 \pm 0.38 ^{dc} | 0.012* |
| Hs-CRP (mg/L) | 22.5 \pm 4.95 ^a | 9.68 \pm 2.74 ^b | 3.3 \pm 0.98 ^c | 2.9 \pm 0.49 ^{dc} | 0.001** |
| TC (mg/dl) | 140.6 \pm 10.1 ^a | 147.1 \pm 7.20 ^a | 154.8 \pm 24.7 ^a | 147.9 \pm 7.64 ^a | 0.805 |
| TG (mg/dl) | 120.2 \pm 18.6 ^a | 121.2 \pm 13.7 ^a | 179.4 \pm 28.6 ^a | 142.3 \pm 18.8 ^a | 0.332 |
| HDL -C(mg/dl) | 37.1 \pm 3.10 ^a | 39.0 \pm 1.53 ^a | 38.0 \pm 2.87 ^a | 41.1 \pm 1.64 ^a | 0.405 |
| LDL-C (mg/dl) | 83.6 \pm 9.11 ^a | 80.1 \pm 6.70 ^a | 83.2 \pm 16.0 ^a | 82.1 \pm 6.07 ^a | 0.767 |
| VLDL-C(mg/dl) | 26.8 \pm 4.70 ^a | 27.3 \pm 2.72 ^a | 30.1 \pm 9.71 ^a | 29.7 \pm 3.86 ^a | 0.439 |

Data are presented as mean \pm standard error; IFN- γ : by using one way ANOVA test; Interferon-gamma; Hs-CRP: High sensitive C-Reactive Protein; TC: Total Cholesterol; TG: Triglycerides; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; VLDL: Very Low Density Lipoprotein; Different letters are significant.* P values ≤ 0.05 is considered to be statistically significant; ** P value < 0.01 : Highly significant.

Table 3: A comparison of mean values of inflammatory and lipid profile markers among CAPs and controls according to body mass index.

| Parameters | Normal < 25 | | Overweight 25-29 | | Obese ≥ 30 | |
|-----------------------|-----------------|------------------|------------------|------------------|------------------|------------------|
| | Mean \pm SE | | Mean \pm SE | | Mean \pm SE | |
| | CAPs No=12 | Control No=15 | CAPs No=18 | Control No=15 | CAPs No=19 | Control No=9 |
| IFN- γ (pg/mL) | 5.18 \pm 0.57 | 3.73 \pm 1.2 | 5.68 \pm 0.41 | 4.14 \pm 0.51 | 6.5 \pm 0.79 | 4.36 \pm 0.98 |
| | 0.010* | | 0.412 | | 0.022* | |
| Hs-CRP (mg/L) | 8.60 \pm 2.59 | 3.23 \pm 0.9 | 9.73 \pm 4.40 | 3.32 \pm 0.6 | 22.5 \pm 4.9 | 4.26 \pm 0.13 |
| | 0.016* | | 0.012* | | 0.013* | |
| TC (mg/dl) | 129 \pm 9.67 | 134 \pm 18.6 | 159 \pm 9.28 | 152 \pm 11.1 | 140.6 \pm 10.1 | 154.8 \pm 24.7 |
| | 0.360 | | 0.635 | | 0.526 | |
| TG (mg/dl) | 92 \pm 15.2 | 130 \pm 27.7 | 150 \pm 19.4 | 154 \pm 26.1 | 122.2 \pm 18.6 | 142.4 \pm 28.6 |
| | 0.256 | | 0.636 | | 0.108 | |
| HDL-C(mg/dl) | 37.5 \pm 2.88 | 44.1 \pm 2.83 | 37.0 \pm 1.74 | 38.1 \pm 1.38 | 38.0 \pm 2.87 | 40.1 \pm 3.10 |
| | 0.173 | | 0.590 | | 0.62 | |
| LDL-C(mg/dl) | 73 \pm 7.59 | 79.6 \pm 7.93 | 97.8 \pm 9.4 | 84.5 \pm 9.42 | 76.2 \pm 9.11 | 85.2 \pm 16.0 |
| | 0.555 | | 0.338 | | 0.664 | |
| VLDL-C (mg/dl) | 18.4 \pm 3.0 | 27.8 \pm 5.98 | 35.5 \pm 3.84 | 31.8 \pm 5.02 | 27.8 \pm 4.71 | 30.7 \pm 9.71 |
| | 0.208 | | 0.566 | | 0.050* | |

Data are presented as mean \pm standard error; using independent sample student's t-test; IFN- γ : Interferon-gamma; Hs-CRP: High sensitive C - reactive protein; TC: Total Cholesterol; TG: Triglycerides; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; VLDL: Very Low Density Lipoprotein; * P values ≤ 0.05 is considered to be statistically significant.

Table 4 illustrates the Pearson correlation coefficient to explain the relationship between studied parameters in obese CAPs. There was a negative weak significant correlation between IFN- γ , and HDL-C ($r=0.456$; $P = 0.040$), and positive non-significant correlations between IFN- γ with Hs-CRP, LDL, and VLDL cholesterol ($P = 0.702, 0.411, \text{ and } 0.478$, respectively).

Discussion

The current study aimed to evaluate IFN- γ cytokine and HsCRP biomarkers in coronary atherosclerotic patients compared to the control group regarding obesity. According to the best of our knowledge studies evaluating in combination, both biomarkers engaged in the pathophysiology of obese atherosclerotic disease are limited. Moreover, which should be underlined, this aims to determine the serum level of IFN- γ cytokine in a group of obese coronary atherosclerotic patients and determine it is a pathophysiological role in those patients. The average age distribution of patients in the current study was mostly in the sixth decade (60); the result seems similar to those of previous studies.^{11,12} This might be the most frequent complications that occur and appear at the mentioned age group. Concerning gender, this study revealed that CAPs percentage in males was slightly higher (51%) than females (48%). These

observations were agreeable to the results obtained by another study.¹³ Hormonal, physiological, and lifestyle differences between females and males play an important role in increasing the risk of disease in males. Previous observational studies also have shown that males exhibit excess risk for cardiovascular disease compared with the age-matched females,¹⁴ suggesting that the immune mechanisms lead to CAD in the male are different from those in females. In contrast, cardiovascular disease accelerates in females after menopause. Some of this apparent protection could be because females exhibit a relatively higher HDL cholesterol concentration than do age-matched males.^{15,16} A family history of heart disease is associated with a higher risk of coronary artery disease, especially if a close relative developed heart disease at an early age.¹⁷ A large number of genetic factors such as those influencing the lipid profile interact with environmental factors to determine overall cardiovascular risk.¹⁸ The present study has shown that 28 (57.1%) of patients were having a family history of coronary artery disease. A similar result was seen in the previous study.¹⁹ The current study has shown that circulating levels of proinflammatory cytokine IFN- γ , as well as acute phase protein Hs-CRP, were significantly higher in the CAPs than those in

Table 4: Correlation between serum level of proinflammatory biomarkers (IFN- γ and Hs-CRP) and Lipid profile parameters (TC, TG, HDL-C, LDL-C, and VLDL-C) in obese CAPs subgroup.

| Parameters | IFN- γ (pg/ml) | Hs-CRP (mg/l) | TC (mg/dl) | TG (mg/dl) | HDL-C (mg/dl) | LDL-C (mg/dl) | VLDL-C (mg/dl) |
|-----------------------|--------------------------|------------------|---------------|---------------|------------------|------------------|-------------------|
| IFN- γ (pg/mL) | r | 0.063 | -0.122 | -0.170 | -0.456 | 0.199 | 0.173 |
| | P value | 0.701 | 0.620 | 0.486 | 0.040* | 0.411 | 0.478 |
| Hs-CRP(mg/L) | r | 0.063 | 0.113 | -0.079 | -0.338 | 0.240 | 0.299 |
| | P value | 0.702 | 0.644 | 0.740 | 0.157 | 0.322 | 0.213 |

The result expressed as Pearson correlation coefficient(r). IFN- γ : Interferon gamma; Hs-CRP: High sensitive-C Reactive Protein; TC: Total Cholesterol; TG: Triglyceride; HDL-C: High Density Lipoprotein-Cholesterol, LDL-C : Low Density Lipoprotein-Cholesterol; VLDL-C: Very Low Density Lipoprotein-Cholesterol; P values ≤ 0.05 is considered to be statistically significant

the controls. Additionally, the above mentioned proinflammatory markers (IFN- γ and Hs-CRP) levels were also higher in the obese CAPs and control than non-obese CAPs and control, This was in agreement with other previous studies,^{20,21} with obese and atherosclerotic patients having increased concentration of proinflammatory biomarkers IFN- γ and CRP levels. The presence of OxLDL triggers the inflammatory response as IFN- γ in the endothelial cells of atherosclerotic patients. Additionally, obesity is accounted for lipid metabolism abnormality, increasing visceral adipose tissue levels cause to increase IFN- γ levels because adipose tissue in obese patients contains abundant numbers of macrophages and T lymphocytes consequently activated T lymphocyte lead to express high levels of IFN- γ .^{23,24} Obesity may also have a direct relationship with the increased Hs-CRP level because inflammation initiated from visceral adipose tissue induces the production of acute phase reactants, particularly CRP.²⁵ Serum CRP level is a sensitive marker of systemic inflammation and may reflect proinflammatory cytokines' amount and activity.¹ It is shown that CRP also has an influence on the process of atherosclerosis through the destruction of endothelial cells, and formation, maturation, and final disruption of atheromatous plaque.²⁶ Moreover, the findings of the study²⁷ suggested that CRP may be accepted as one of the indexes to estimate the degree of coronary artery disease. Their findings supported the present results, in which Hs-CRP level elevated significantly in CAPs than controls, which might designate that happening and development of plaque is engaged with inflammation. The current study revealed that the mean concentration of the investigated lipid profile levels among obese CAPs and control were decreased than non-obese CAPs and control, with no significant differences. The results were incomparable with other previous studies,^{28,29} in which lipid

profile increased among obese and atherosclerotic patients. The mentioned level of lipid profile might be due to about 45 (91%) of patients receiving statins for lowering lipid profiles. Interestingly, the results of the present study have shown a weak negative significant correlation between pro-atherogenic marker IFN- γ with anti-atherogenic lipid HDL-C. In contrast, IFN- γ has a positive correlation with Hs-CRP and LDL-C in obese CAPs; results were in line with other previous studies in this field³⁰⁻³² in which IFN- γ reduces the level of anti-atherogenic HDL-C. The elevation of mentioned pro-atherogenic markers, particularly the LDL-C level, was correlated with an increased risk for atherosclerosis. At the same time, HDL-C has a reverse relation with atherosclerosis development, which acts as an atherogenesis inhibitor and has a role in reverse cholesterol transport or anti-inflammatory, antioxidant, and vascular protecting properties. It is likely that HDL-C may act as cardiovascular health biomarkers.³³ This study shows that the risk of coronary atherosclerosis is correlated with serum levels of IFN- γ in obese subjects. This indicates that the determination of IFN- γ levels in obese atherosclerotic subjects may predict their potential risky as an important parameter in the early detection of developing coronary artery disease. One of the limitations of this study is that the lipid profile levels among overweighted and obese subjects were normal. It may be related to using lipid-lowering medications, which may influence the obtained results.

Conclusion

Serum proinflammatory markers IFN- γ , Hs-CRP, and LDL-C level have pathophysiological roles in obese coronary atherosclerotic patients as a pro-atherogenic biomarker. They could be used clinically as a predictor for cardiovascular disease progression, in contrast, HDL-C level believed to be an anti-atherogenic biomarker.

Competing interests

The authors declare no competing interests.

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