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Original article

Effect of Coronary Reperfusion Therapy on Inflammatory Markers, Adiponectin and Insulin Resistance in Ischemic Patients

Hamed Mohamed Osman[1], Khaled Ahmad El Kashab[2], Amani M. El Amin Ali[3*], Ahmed MagdyElebiary[3] , Ahmed Desoky Badawy[4]

[1]Department of Medical Physiology, Faculty of Medicine, Al Azhar University, Egypt.

[2]Department of Cardiology, Faculty of Medicine, Fayoum University, Egypt.

[3]Departement of Medical Physiology, Faculty of Medicine, Fayoum University, Egypt.

[4]Department of Medical Physiology, Faculty of Medicine, 6th October University, Egypt.

ABSTRACT

Background: Patients who underwent percutaneous coronary interventions (PCI) and surgical coronary artery bypass grafting (CABG) for coronary artery disease may have inflammatory response. Insulin resistance-associated dysfunction of lipid metabolism can promote both systemic and local inflammatory responses that participate in the development of coronary artery disease. **Objective:** The aim of our work is to determine the changes in serum adiponectin level, high sensitive C-reactive protein in patients who underwent PCI and surgical CABG for coronary artery disease and compare the effect of both revascularization procedures on these parameters in non-diabetic ischemic patients after one month. Also we investigated whether or not there was a relation between their levels and insulin resistance. **Materials and Methods:** 40 patients with ischemic heart disease who underwent the procedure of reperfusion therapy are reevaluated one month after intervention by either PCI or CABG. Serum adiponectin, insulin & high sensitive C-reactive protein were measured and insulin resistance was assessed using HOMA-IR index. **Results:** High sensitive C reactive protein, Insulin and adiponectin levels decreased significantly in patients after PCI with p-value <0.05.One month after revascularization, high sensitive C reactive protein and adiponectin levels were significantly higher in patients exposed to CABG in comparison to patients exposed to PCI. Insulin resistance as indicated by HOMA-IR was elevated in patients one month after CABG with p-value <0.05. **Conclusion:** PCI causes less reperfusion injury compared to CABG procedure depending on high sensitive C-reactive protein as predictor of reperfusion injury after revascularization by PCI in ischemic patients.

KEYWORDS: Adiponectin, Coronary artery revascularization, High sensitive C-reactive protein, Insulin resistance.

INTRODUCTION

Acute coronary syndrome (ACS) has been progressed as a convenient functioning term that refers to a spectrum of conditions compatible with acute myocardial ischemia and/or infarction due to an abrupt reduction in coronary blood flow [1]. Both conservative and invasive treatment strategies have been developed for the treatment of ACS. Either a positive stress test or persistent/recurrent angina is followed by cardiac catheterization with revascularization, which was either by percutaneous coronary interventions (PCI) or surgical coronary artery bypass grafting (CABG) [2]. Ischemic post-conditioning (IPostC) has developed as a hopeful method for myocardial protection against ischemia reperfusion injury (IRI) both in experimental and in clinical settings. Enrichment of endogenous nitric oxide (NO) is one of the most important mechanisms by which IPostC confers cardio-protection [3].

Even if circulating adiponectin is produced chiefly from adipose tissue, this adipokine is also expressed and secreted in cardiomyocytes [4]. Additionally, cardiomyocyte-derived adiponectin is biologically active in protecting cells against IRI by paracrine / autocrine activation of adiponectin receptors [5]. Adiponectin stimulates peripheral insulin sensitivity, impedes liver gluconeogenesis and shows anti-atherogenic and anti-inflammatory properties [6]. Decreased plasma adiponectin levels are observed in patients with diabetes, metabolic syndrome, and coronary artery disease and this may show a crucial role in the progress of insulin resistance [7].

Insulin resistance (IR) plays risky roles in the progress of cardiovascular diseases, such as atherosclerosis, hypertension and restenosis [8]. Hyperinsulinemia give the impression to be preservative to risks associated with lipid abnormalities, plus increased LDL-C and lipoprotein B. Hyperinsulinemia is concomitant with increased plasminogen activator inhibitor (PAI)-1 [9]. Moreover CRP has been reported to be a strong predictor of future cardiovascular disease [10]. High-sensitivity CRP (hs-CRP) is more precise than standard CRP when measuring baseline concentrations and in chronic inflammation. hs-CRP has been authorized by several guidelines as a biomarker of atherosclerotic cardiovascular disease risk [11]. In patients with acute coronary disease, CRP level predicts mortality and cardiac complications [12].

So the present work aims to find out if there is a change in adiponectin level, hs CRP and insulin resistance in patients who underwent PCI versus CABG for coronary artery disease (CAD) diagnosed by coronary angiography and to compare the effect of both revascularization procedures on these parameters in non-diabetic ischemic patients after one month follow up.

MATERIALS AND METHODS

This cohort prospective study was designed and conducted on 40 non-diabetic patients who are presented with ischemic heart disease diagnosed according to AHA/ACC (the American Heart Association and the American College of cardiology 2014) CAD was characterized by significant (>50%) luminal diameter narrowing among one of the major coronary arteries or its branches 1, 2 or 3-vessels disease, proved by coronary angiography. All patients were recruited from outpatient clinic Cardiology Department, Intensive Care Unit and Cardiothoracic Unit in Fayoum University Hospital after obtaining an approval from Research Ethics Committee in Fayoum Faculty of Medicine. Before patients being enrolled in the study, and after full explanation of the purpose of the study, written consent was obtained from each subject.

All patients were exposed to careful full detailed history and clinical examination included vitals, i.e., pulse, blood pressure, and detailed examination of the cardiovascular system to exclude the following: reduced left ventricular ejection fraction (<40%) and underlying infections, inflammatory or malignant diseases and treatment with anti-inflammatory or immunosuppressive drugs. Patients were evaluated by ECG, echocardiography, coronary angiography and routine laboratory investigations.

Patients were divided equally into two groups each of 20 patients.

Group I: Ischemic patients (20 males) their mean age was 55.0± 4.1 years who had undergone PCI. Patients with unstable angina referred for PCI as treatment of choice in patients with 1 and 2 vessel diseases without stenosis in the left anterior descending artery (LAD) , coronary stents are delivered and then using guiding catheters and coronary guide wires. Femoral artery catheterization is most common [13].

GroupII: Ischemic patients (18 males and 2 female) their mean age was 54.2±5.8 years who had undergone surgical revascularization CABG. Patients with 3 vessel disease with stenosis >70% with large ischemic territory or 2 vessels region stenosis >70% including proximal LAD or Left main artery stenosis >50%, diagnosed by coronary angiography had undergone CABG. Saphenous vein graft, internal mammary conduits are remarkably resistant to atherosclerosis. The internal mammary artery (IMA) performs best when used to bypass the left anterior descending artery [14]. These patients were operated on using a standard cardiopulmonary bypass technique, aortic and right atrial (two stage) cannulation, with membrane oxygenator, moderate hemodilution, and mild systemic hypothermia (32–34°C).

Blood samples and laboratory assay:

Biochemical tests were performed on blood samples collected after overnight fast (12 hours). Venous blood was drawn, prior to coronary revascularization procedures and one month after the procedure. After centrifugation of the specimen, serum and plasma were frozen immediately at (-20° C) until biochemical analysis was performed.

Fasting insulin was assayed by using human insulin ELISA kit according to the instructions from the manufacturer Calbiotech (Austin , Spring Valley USA) assay range < 25 µlU/ml.

The HOMA-IR index was calculated on the basis of levels of fasting glucose and plasma insulin. We used it as an index of insulin resistance in accordance with the following equation, HOMA-IR = fasting glucose (mmol/l) × fasting insulin (µU/ml) /22.5 [15].

Hs-CRP was measured by using human hs-CRP ELISA kit according to the instructions from the manufacturer immunospectrum (Owens mouth Ave. Suite Canoga Park USA) assay range 68 to 8200 ng/ml. Plasma adiponectin was measured by using human adiponectin ELISA Kit(Harry S Truman Blvd St. Charles USA) assay range from 2 to 15µg/ml.

Statistical Analysis:

- Data were collected and coded to facilitate data manipulation and double entered into Microsoft Access and data analysis was performed using SPSS software version 18 in windows 7.
- Simple descriptive analysis in the form of numbers and percentages for qualitative data, and arithmetic means as central tendency measurement, standard error as measure of dispersion for quantitative data, and inferential statistic test:

- For quantitative non parametric data

- Mann-whitney test in comparing two independent groups.
- Wilcoxon tests used in comparing two groups of dependent data
- For qualitative data
- Chi square test to compare two of more than two qualitative groups.
- Bivariate Pearson correlation test to test association between quantitative variables.
- The level $P \leq 0.05$ was considered the cut-off value for significance.

RESULTS

Group I: (Patients undergoing PCI):

One month after PCI plasma hs-CRP levels were significantly decreased (P<0.002) when compared to its level before PCI. Also there was a significant decrease in adiponectin levels one month after PCI (P<0.001) when compared to its levels before revascularization (Table 1).

In this study, we have chosen the simple HOMA-IR equation to calculate IR. We have found that there was a significant decrease in HOMA-IR one month after PCI (p<0.004) compared to its level before PCI indicating decrease insulin resistance after PCI (Table 1).

Table 1: Comparison of the study variables before and one month after PCI

Variables		**PCI (N=20)**	**p-value**
		Mean ± SE	
hs-CRP (ng/ml)	Before	67.7±6.8	0.002*
	After	57±6.9	
Adiponectin (µg/ml)	Before	5.83±0.069	0.001*
	After	5.69±0.06	
Insulin (µIU/ml)	Before	33.9±9.1	0.004*
	After	3.5±0.71	
Blood glucose mg/dl	Before	127.5±8.3	0.01*
	After	101.5±4.3	
HOMA-IR	Before	13.6±3.8	0.004*
	After	0.86±0.19	

*statistical significance with p-value <0.05 between before and one month after PCI. N=number.

Also we carried out a correlation analysis between study variables one month after PCI in all subjects. There is statistical significance positive correlation with p-value <0.05 between hs-CRP and each of adiponectin and glucose level one month after intervention, which indicated increase in glucose level and adiponectin is associated with increase in hs-CRP level (Table 2).

Table 2: Correlation between the study variables one month after PCI

Variables			
	R	**p-value**	**Sig.**
HS-CRP &adiponectin	0.60	0.005	HS
HS-CRP & glucose	0.45	0.04	S
HS-CRP & insulin	0.32	0.2	NS
HS-CRP & HOMA-IR	0.36	0.1	NS

Adiponectin& glucose	0.11	0.6	NS
Adiponectin& insulin	0.25	0.3	NS
Adiponectin& HOMA-IR	0.27	0.3	NS

HS= highly significant, S = significant, NS= non significant, p<0.05- significant.

Group II: (Patients undergoing CABG):

There are no significant changes in hs-CRP and adiponectin levels in ischemic patients before and after revascularization. However,insulin level was significantly increased one month after CABG (p<0.004) as compared to its level before CABG. Also we can see that HOMA-IR which reflect insulin resistance, were significantly increased one month after CABG (p<0.003) compared to its level preoperative, indicating increase insulin resistance after CABG (Table 3). Moreover we can see the significant positive correlation with p-value <0.05 between hs-CRP and each of HOMA-IR and plasma levels adiponectin level one month after intervention (Table 4).

Table 3: Comparison of study variables before and one month after CABG

Variables		**CABAG** (N=20) **Mean ± SE**	**p-value**
HS-CRP (ng/ml)	Before	75±6.9	0.06
	After	86±4.3	
Adiponectin (µg/ml)	Before	6.16±0.15	0.1
	After	5.94±0.05	
Insulin (µlU/ml)	Before	4.2±0.72	0.004 †
	After	14.9±3.1	
Blood glucose mg/dl	Before	127.7±3.9	0.001 †
	After	155.4±5.2	
HOMA-IR	Before	1.28±0.21	0.003 †
	After	6.2±1.4	

† statistical significance with p-value <0.05 between before and one month after CABG. N=number.

Table 4: Correlation between study variables one month after CABG

Variables			
	R	**p-value**	**Sig.**
HS-CRP &adiponectin	0.52	0.02	S
HS-CRP & glucose	0.54	0.02	S
HS-CRP & insulin	0.52	0.02	S
HS-CRP & HOMA-IR	0.53	0.02	S
Adiponectin& glucose	0.27	0.2	NS
Adiponectin& insulin	0.09	0.7	NS
Adiponectin& HOMA-IR	0.13	0.6	NS

S = significant, NS= non significant, p<0.05- significant.

PCI (group I) versus CABG (group II):

Interpretation to the baseline characteristics, there was no statistically significant difference with p-value >0.05 between group I (PCI) and group II (CABG) as regards age and sex of patients, which indicate proper matching between study groups.

There was no significant difference in plasma hs-CRP levels before revascularization in both groups PCI and CABG (P>0.05). While one month after revascularization, hs-CRP level was significantly higher ($p < 0.001$) in patients undergoing CABG than its value in PCI group (Table 5). So we can consider that PCI causes less reperfusion injury compared to CABG procedure depending on hs-CRP as predictor of reperfusion injury after revascularization by PCI in non-diabetic ischemic patients.

The preoperative value of adiponectin was significantly higher ($p < 0.05$) in patients undergoing CABG compared to patients undergoing PCI. One month after revascularization adiponectin levels still significantly higher in patients undergoing CABG (p<0.003) compared to its levels in patients undergoing PCI (Table 5).

Also, table 5 shows that before revascularization the level of glucose was insignificantly different in both groups (P>0.05), but the insulin level was significantly higher in patient underwent PCI compared to CABG group (P<0.002). Moreover HOMA-IR was significantly higher in PCI group compared to CABG group (P<0.003). Which mean that patients underwent PCI had more insulin resistance than patients who underwent CABG before revascularization. But one month after revascularization, insulin and glucose levels were significantly increased in CABG (p<0.001) compared to PCI levels. Furthermore HOMA-IR levels were significantly increase in CABG (P<0.001) when compared to its level in PCI. Indicating that CABG aggravates insulin resistance than PCI (Table 5).

Table 5: Comparison of study variables between PCI and CABG groups

Variables		**PCI** (N=20) **Mean ± SE**	**CABAG** (N=20) **Mean ± SE**	**p-value**
hS-CRP (ng/ml)	Before	67.7±6.8	75±6.9	0.5
	After	57±6.9	86±4.3	0.001 ‡
Adiponectin (µg/ml)	Before	5.83±0.069	6.16±0.15	0.05 ‡
	After	5.69±0.06	5.94±0.05	0.003 ‡
Insulin (µlU/ml)	Before	33.9±9.1	4.2±0.72	0.002 ‡
	After	3.5±0.71	14.9±3.1	0.001 ‡
Blood glucose (mg/dl)	Before	127.5±8.3	127.7±3.9	0.9
	After	101.5±4.3	155.4±5.2	<0.001 ‡
HOMA-IR	Before	13.6±3.8	1.28±0.21	0.003 ‡
	After	0.86±0.19	6.2±1.4	0.001 ‡

‡ Statistical significance with p-value <0.05 between PCI and CABG. N=number.

DISCUSSION

Reperfusion therapy is an essential treatment to increase blood flow to the ischemic area, but may cause harmful tissue injury called IRI [16]. The present study aimed to find out if there is change in adiponectin level, hs-CRP and insulin resistance in patients who underwent PCI and surgical CABG for CAD and to compare the effect of both revascularization procedures on these parameters in non-diabetic ischemic patients one month after these procedures.

There are no statistically significant differences between ischemic patients need PCI versus CABG regarding hs-CRP at the start of the study. The pre-revascularization high hs-CRP level is more a predictor of inclusive cardiovascular risk [17]. However, one month after revascularization our results show that hs-CRP level is significantly lower among ischemic patients revascularization by PCI in comparison to patients of multi-vessels disease that needed CABG. When interpreting these results, we can consider that PCI causes less reperfusion injury than CABG.

These results strengthen the argument that in CABG patients, epicardial adipose tissue represents a negative

influence on both cardiovascular outcome and myocardial function. Hs-CRP levels indicate a worse prognosis in patients with acute coronary syndromes [12]. The elevated inflammatory marker hs-CRP 6 months after PCI was associated with late angiographic in-stent restenosis [18]. Moreover, elevated hs-CRP level independently predicts adverse outcomes as patients with the highest hs-CRP level had more coronary events than patients with the lowest hs-CRP [19].

In Fracassi study, a higher risk of major adverse cardiovascular events after PCI was reported in patients who had significantly higher CRP levels [20]. But in our study, we depend on biochemical follow up rather than morbidity and mortality. In contrast, the hs-CRP levels were not persistently elevated, but returned to baseline values one month after PCI [21].

As regards adiponectin, there is significant lower level of adiponectin before revascularization by PCI compared to CABG group. Moreover, there is statistically significant lower adiponectin level in patients after revascularization by PCI compared to CABG group. And in both groups there was a positive correlation between hs-CRP and adiponectin. There are associations between high levels of adiponectin and worse clinical outcome due to increased disease severity as in patients with acute coronary syndrome [22], but our patients were stable ischemic. Patients with highest adiponectin levels were more likely to be hospitalized for heart failure than those in the lowest level [23]. Also the patients with stable CAD, with high adiponectin level display a worse clinical profile [24].

It has been suggested that patients with heart failure may develop an adiponectin resistance with increased adiponectin concentrations, but reduced expression of receptors. As an alternative, high level of adiponectin may represent a hallmark of wasting and sarcopenia [25]. In addition, when ventricular dysfunction develops, adiponectin synthesis and release may be stimulated by natriuretic peptides and/or by metabolic/inflammatory mediators [26].Plasma adiponectin were shown to be declined after myocardial ischemia reperfusion injury [27]. Also adiponectin levels in non-diabetic patients decreased with IR compared to the controls [28]. The low adiponectin especially during the early post-PCI period, carries the risk for impaired coronary reperfusion [29].

Higher adiponectin is reliably related to poor prognosis [6]. Plasma adiponectin levels are an inverse predictor of cardiovascular outcome in patients with end-stage renal disease and stroke [30]. Serum adiponectin levels are also inversely related to the severity of CAD in non-diabetic patients [31]. Moreover, the reperfusion-induced decrease in adiponectin, thus it may serves as a useful biomarker or a drug target in conditions complicated by ischemia-reperfusion injury [32]. Our study also provides evidence that insulin resistance was significantly decreased one month after PCI procedure in contrast to CABG which associated with significant increase insulin resistance. Moreover, we found a significant correlation between HOMA-IR and the plasma levels hs-CRP in patients who underwent CABG. Suggest hazards effect of CABG on insulin resistance. Also, Vikram found that hs-CRP concentrations significantly correlate with insulin resistance [33].

Prolonged decreases of endothelial nitric oxide Synthase (eNOS) lead to decreased bioavailability of nitric oxide (NO), which acts as vascular protection by inhibiting inflammation, oxidation, vascular smooth muscle cell proliferation, and migration [34]. Repeated hyper-insulinemia due to increased level of triglycerides, FFAs and LDL and decreased HDL, donates to endothelial dysfunction and interrupts nitric oxide (NO) secretion, increases reactive oxygen species (ROS) and free radicals formation, and interruptions of adhesion molecule expression of chemokine and cytokine release [35]. There was a direct correlation between insulin resistance and the accelerated progression of atherosclerosis in obese subjects [36]. Obtainable evidence advocates that systemic inflammation, as evidenced by elevated hs-CRP in patients underwent CABG may be of etiologic importance in insulin resistance and diabetes.

CONCLUSION

Hs CRP can be used as predictor of reperfusion injury after revascularization by PCI in non-diabetic ischemic patients. Also adiponectin is useful in assessment of the severity of coronary atherosclerosis, as both decreased one month after procedure. Reperfusion may play critical roles in the development of CVD, such as atherosclerosis and restenosis. Insulin resistance as indicated by HOMA-IR elevated in patients one month after CABG. Also, we found a significant correlation between HOMA-IR and the plasma levels hs-CRP. When interpreting these results, we can consider PCI causes less reperfusion injury than CABG. The effects of lifestyle modifications and drugs on hypo-adiponectinemia and insulin resistance need further studies. When interpreting these results, it should be taken in consideration that the possible ethnic variability in the Egyptians may lead to confounding results.

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*Corresponding author:Amani M. El Amin Ali
E-Mail:elamin_amani@yahoo.com