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Original article

Serial changes in the serum levels of leptin, homocysteine, galectin-3, total phospholipids and hexosamines among patients undergoing coronary artery bypass grafting

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Abstract

Background: Coronary artery disease (CAD) is the most common cardiovascular disorder in adults. This study was performed to elucidate the role of active leptin, homocysteine, galectin-3, total phospholipids, total, bound, free hexosamines, free-to-bound hexosamines ratio in the pathogenesis of chronic myocardial ischemia and studying the effect of coronary artery bypass grafting (CABG) on their serum levels.
Methods: A prospective case control study was carried out on 100 ischemic heart disease male patients undergoing elective CABG and 25 healthy males. Serum levels of total phospholipids, total and free hexosamines, were estimated using spectrophotometric methods, while, serum levels of active leptin, homocysteine and galectin-3 were estimated using ELISA assay kit.
Results: Significant higher serum active leptin, homocysteine, galectin-3, free hexosamines and free to bound hexosamines ratio levels preoperatively when compared with the control group ($p < 0.01$ for all) with significant lowering of their serum levels following CABG ($p < 0.01$ for all) except for active leptin. Significant lower serum total phospholipids, total and bound hexosamines levels preoperatively when compared with the control group ($p < 0.01$ for all) with significant elevations in their serum levels following CABG ($p < 0.01$ for all).
Conclusions: High active leptin, homocysteine, galectin-3, free and free to bound hexosamines ratio and low total phospholipids, total and bound hexosamines play an important role in the pathogenesis of myocardial ischemia. The serum levels of homocysteine, galectin-3, hexosamines and total phospholipids, but not active leptin are significantly lowered following CABG.

Keywords: Leptin; Homocysteine; Galectin-3; Phospholipids; Hexsoamines; CABG

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1. Introduction

Coronary artery disease (CAD) is the most common cardiovascular disorder in adults. It is caused by the build-up of cholesterol deposits in the wall of the coronary arteries. CAD often results in heart attack (myocardial infarction) or chest pain (angina pectoris), even in the absence of prior symptoms [1]. Treatment for CAD can include changes in life style, diet modification, weight reduction, and cholesterol reduction [2], as well as control of diabetes and hypertension. Smoking cessation is also considered as an essential regimen [3]. Many patients can be adequately treated with medications. Some individuals, however, will require invasive treatments such as percutaneous coronary intervention (PCI) or coronary artery bypass grafting surgery (CABG) [4]. Cardiopulmonary bypass (CPB) is still used in most CABG surgery. Hemodynamic and biochemical changes possibly caused by the CPB have been not elucidated in details in literature [5].

Leptin is an adipose tissue derived hormone that plays a central role in regulating human energy homeostasis. The role of leptin in regulating blood pressure, activating the sympathetic nervous system, insulin resistance, platelet aggregation, arterial thrombosis, angiogenesis, and inflammatory vascular responses suggests that leptin may have a close relationship with the development of CAD [6]. Because obesity and these metabolic syndrome traits predict CAD, one might expect elevated leptin levels to be associated with ischemic heart disease (IHD) risk. Elevated leptin indicates resistance to its beneficial action on appetite control and energy expenditure. Such an association would potentially make leptin metabolism and action a target for therapeutic interventions and leptin levels a useful predictor of IHD risk [7].

Hexosaminidase is responsible for removing the hexosamine, N-acetyl glucosamine (O-GlcNAc), from proteins, releasing it into the free form. Elevated hexosaminidase expression significantly reduces the protein bounded form of O-GlcNAc and increases the free form of O-GlcNAc leading to augmented post-ischemic cell death and antagonizes post-ischemic cardiac myocyte survival [8].

Homocysteine is a sulfur-containing amino acid produced in the metabolism of the essential amino acid methionine [9]. Homocysteine stimulates atherosclerosis by causing oxidative endothelial damage, altering the coagulation of blood, and destruction of vascular matrix, thus promoting the thrombus-embolic diseases [10].

Galectin-3 “Gal-3” belongs to the family of β-galactoside binding proteins with an extended N-terminal region and C-terminal domain, which is responsible for lectin activity [11]. In atherogenesis, Gal-3 has been reported to have a multifaceted influence on both plaque formation and its destabilization [12]. It propagates vascular inflammation, induces phenotypic changes in macrophages and supports transmigration of monocytes into the vascular wall [13].

Phospholipids have amphiphilic properties, which might play a mediating role in the transport and removal of hydrophobic neutral lipids, in particular of cholesterol esters, from vessel walls. Accordingly, high density lipoprotein “HDL” with reduced phospholipid content has been found to be a poor receptor of cell cholesterol. Because of their surface active properties, phospholipids also play an important role at all stages of coagulation and therefore are probably essential for interactions between non-polar lipids and polar coagulation proteins. Such interactions may be important in view of the contribution of thrombosis to arteriosclerosis, of the thrombotic origin of myocardial infarction and unstable angina, and of the poor lysability of platelet-rich thrombi [14].

Based on literature, the present study assesses and confirms the role of a group of biochemical markers, in the form of active leptin, homocysteine, galectin-3, total phospholipids, total, bound, free hexosamines and free-to-bound hexosamines ratio in the pathogenesis of chronic myocardial ischemia and explore whether CABG could change their serum levels or not since this couldn't be traced in literature.

2. Patients and methods

2.1. Participant patient population

This is a prospective case control study which was carried out from December 2011 to March 2016 in the department of Cardiothoracic surgery-Faculty of Medicine- Assiut University. The study included 100 patients who underwent CABG and formed the study group (group 1). These patients were compared with 25 age-matched, apparently healthy males forming the control group (group 2). The study was approved by university hospital ethics committee and informed consents were obtained from the included patients.

2.2. Exclusion criteria

Patients with previous cardiac surgery, ejection fraction less than 40%, chronic renal insufficiency (serum creatinine >1.7 mg/dl) or renal failure on dialysis or use of steroids were excluded from the study.

2.3. Data collections

For each included patient, complete history taking, general and systemic examination, E.C.G, chest X-ray and echocardiography were done; hemodynamic data were recorded as regard heart rate, arterial blood pressure and central venous pressure preoperative, 30 min, one hour and six hours postoperative. This is in addition to routine blood analysis preoperatively in the form of complete blood count, liver and kidney function tests, serum sodium and potassium.

2.4. Laboratory measures

Three cc venous blood was drawn from all patients (preoperative and 15 days postoperative) and control group, on plane tubes, for serial assays of active leptin, total and free hexosamines, homocysteine, galectin-3 and total phospholipids. Blood samples were then centrifuged at 3500 rpm for 15 min at 4 °C and the sera were transferred into 1 ml cryotubes, and stored at −80 °C for later analyses.

Serum human active leptin (DSL-10-23100 supplied by diagnostic systems laboratories, Inc.), serum galectin-3 levels were determined using human galactin-3 ELISA kit (WKEA MED supplies corp. USA) according to manufacturer's protocol [provided by WKEA MED supplies corp. New York. USA] and serum homocysteine levels were measured using an enzyme-linked immune-sorbent (ELISA) assay kit, provided by Chongqing Biospes Co., Ltd. Paradise Walk, Jiangbei District, Chongqing, 400020, Chin. All previously mentioned biochemical markers were measured using enzyme-linked immune-sorbent assay (ELISA) multiskan EX microplate photomter, thermo scientific, STAT FAX-2100, USA.

Total phospholipids using kit provided from ELITECH Diagnostic, catalog no. 0030, total hexosamines were estimated according to Gatt and Berman method [15] and free hexosamines were estimated as for total hexosamines after precipitation of plasma proteins by 10% trichloroacetic acid “TCA”. All previously mentioned biochemical markers were measured using T60 UV visible spectrophotometer (PG INSTRUMENTS LIMITED, alma park wibtoft, Leicester shreshire, England. LE17SBE. Serial No. 20-1650-01-0010).

2.5. Anesthesia technique

Anesthetic management was uniform in all patients. All patients were premedicated with intravenous midazolam (0.03 mg/kg) 30 min before the operation. Anesthesia was induced with fentanyl (3 μg/kg) combined with propofol (2 mg/kg). Endotracheal intubation was performed after achieving muscle relaxant with recuronium bromide (1 mg/kg). Mechanical ventilation was used to maintain eucapnia. Anesthesia was maintained by using continuous infusion of fentanyl (1 μg/kg/hour) and propofol (2–8 mg/kg/hour). Fentanyl infusion was continued postoperative in the intensive care unit (I.C.U).

2.6. Surgical procedure

All patients had median sternotomy. Standard cannulation was done. An initial dose of 400 μg/kg heparin was used to obtain an activated clotting time. Range blood pressure of 50–70 mmHg and blood flow 2–2.4 L/min. Priming solution contains mannitol and heparin. Hypothermia for 25–30 min. Cold (4 °C) crystalloid cardioplegic arrest was used after aortic cross clamping. Coronary bypass grafting was done using venous and arterial conduits. Flow up in the I.C.U for the hemodynamic changes in the heart rate, arterial blood pressure and central venous pressure. Antipyretics and potent antibiotic therapy were given. Before discharge the patient must meet the followings: aware, impulsive breathing, detached endotracheal tube.

2.7. Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS-version 17) software. The results were expressed as mean ± standard deviation. One way ANOVA (analysis of variance) test was used to compare more than two groups as regard quantitative variable (LSD = least significant difference). Pearson correlation analysis was used to evaluate the correlations between different parameters. P values of less than 0.05 were considered significant.

3. Results

3.1. Baseline characteristics

All patients were males with their mean age 51.52 ± 13.76 years and their mean body mass index (BMI) 25.43 ± 2.33. The mean bypass and whole surgery times were 142.78 ± 7.22, 344.5 ± 25.8 min respectively, whereas the mean (I.C.U) stay and ward stay were 2.48 ± 0.51and 13.17 ± 1.67 days respectively (Table 1). No deaths in the studied patients and all the patients involved completed the study.

3.2. Perioperative hemodynamic changes

The mean ± SD of some hemodynamic parameters of the patients preoperatively, 30 min, one hour and six hours postoperatively, were presented in Table 2 and Fig. 1, which reveal significant hemodynamic changes regarding the heart rate, arterial blood pressure and central venous pressure, preoperative versus postoperative recordings.

3.3. Serial serum levels of active leptin, homocysteine, galectin-3, total phospholipids, total, bound, free hexosamines, free-to-bound hexosamines ratio

Results of the serum levels of active leptin, homocysteine, galectin-3 and total phospholipids, both preoperatively and postoperatively compared with the control group were presented in Table 3. Preoperative serum active leptin, homocysteine and galectin-3 levels were significantly higher in the CABG group than in the control group. These levels decreased significantly after the operation without reaching the serum levels in the control group. The only exception is the active leptin which revealed no significant serum level changes postoperatively. In addition, there were significant lower serum total phospholipids levels preoperatively when compared with the control group. These levels showed significant postoperative elevations without reaching the levels of the control group. Results of the serum levels of hexosamines (total, free, bound, free to bound ratio), both preoperatively and postoperatively compared with the control group were presented in Table 4. Preoperative serum free hexosamines levels and free to bound hexosamines ratio were significantly higher in the CABG group than in the control group. These levels decreased significantly after the operation without reaching the serum levels in the control group. In addition, there were significant lower serum total and bound hexosamines levels preoperatively when compared with the control group. These levels showed significant postoperative elevations without reaching he levels of the control group.

4. Discussion

The literature offers no detailed data about the effects of CPB and CABG on hemodynamic changes [5]. In our study, the hemodynamic parameters of the studied patients including heart rate, arterial blood pressure and central venous pressure were recorded, the mean heart rate was significantly higher one hour postoperatively when compared with the heart rate preoperatively, 30 min and six hours postoperatively ($p < 0.01$). The mean arterial blood pressure was

Table 1
Baseline characteristics of patients.

Variables	Minimum	Maximum	Mean ± SD
Age (years)	33.00	71.00	51.52 ± 13.76
BMI	21.00	30.00	25.43 ± 2.33
Time of bypass (Min)	130.00	157.00	142.78 ± 7.22
Time of surgery (Min)	310.00	390.00	344.5 ± 25.8
ICU stay (days)	2.00	3.00	2.48 ± 0.51
Ward stay (days)	11.00	16.00	13.17 ± 1.67

Table 2
Recorded hemodynamic parameters of the patients preoperative, 30 min, one hour and six hours postoperative, using one way analysis of variance "ANOVA" followed by LSD multiple comparisons.

Hemodynamic parameters	Before	30 min	One hour	Six hours	P-value
Heart rate "Beat/min"	85.4 ± 4	78.3 ± 4.4	94.7 ± 3.8	83.1 ± 3	0.000**
Arterial Blood Pressure "mmHg"	85.6 ± 2.8	75.1 ± 2.6	67.9 ± 2.7	70.9 ± 1.3	0.000**
Central Venous Pressure "mmHg"	9.1 ± 0.3	9.1 ± 0.3	8.1 ± 0.3	8.7 ± 0.2	0.000**

*Indicate significant change at $P < 0.05$; ** indicate significant change at $p < 0.01$; *** indicate significant change at $p < 0.001$. NS means non significant (($p > 0.05$).

significantly lower one hour postoperatively when compared with the preoperatively, 30 min and six hours postoperatively ($p < 0.01$). The mean central venous pressure was significantly lower one hour postoperatively versus the preoperative, 30 min and six hours postoperatively ($p < 0.01$). These findings were in agreement with Aydin et al. [5].

The findings of our study revealed a significant higher serum active leptin, homocysteine and galectin-3 levels with significant lower serum levels of total phospholipids among the IHD patients preoperatively when compared with the control group. These findings confirm that these biochemical parameters play an essential role in the pathogenesis of chronic cardiac ischemia with different mechanisms.

For leptin, our findings were in agreement with Wolk et al. [16] and Khafaji et al. [17]. A Study done by Stangl et al. [18] found that patients with CAD exhibited higher serum leptin concentrations than controls matched for age, gender and BMI, suggesting that leptin could contribute to the development of cardiovascular disease, possibly via activation of the sympathetic nervous system. Vavruch et al. [19], reported that high leptin levels were related to increased risks of IHD independently of traditional risk factors in men.

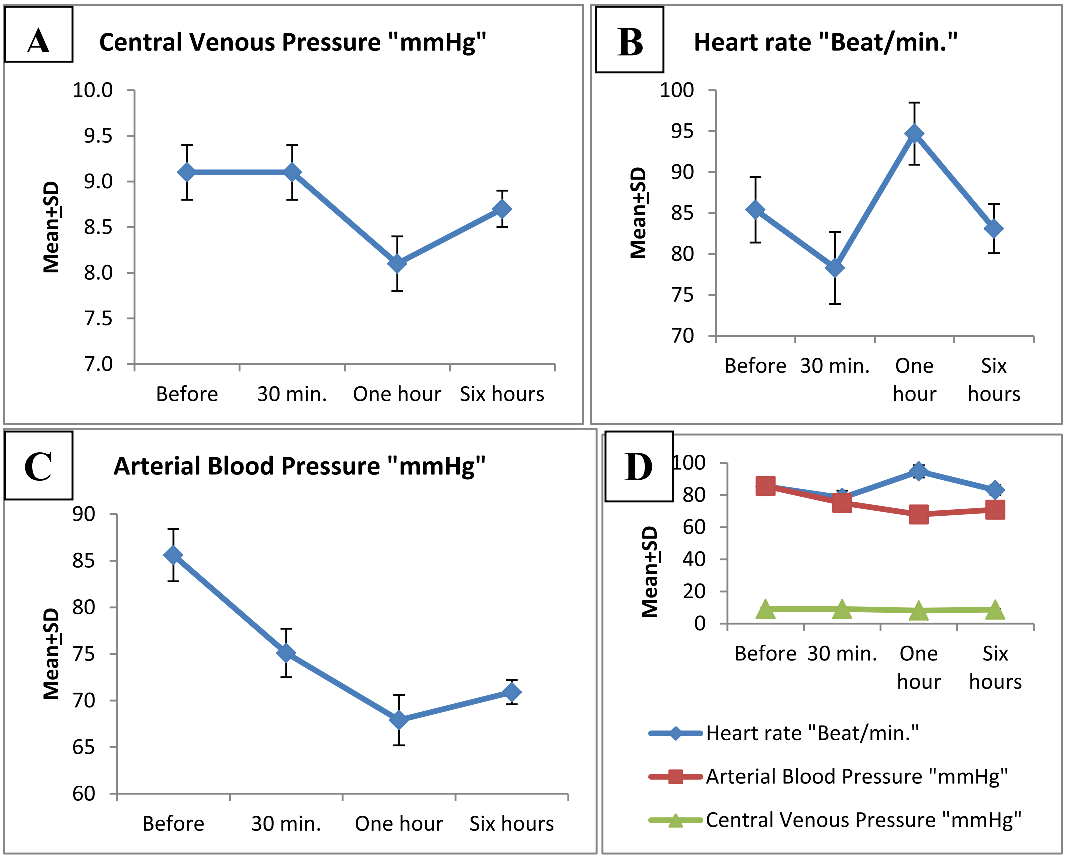

Fig. 1. Comparison of the mean hemodynamic parameters of the patients preoperative, 30 min, one hour and six hours postoperative. A: Central venous pressure "mmHg", B: Heart rate "beat/min", C: Arterial blood pressure "mmHg", D: The three hemodynamic parameters all together.

Table 3
Comparison of the serum levels of active leptin, homocysteine, galectin-3 and total phospholipids preoperative and postoperative versus the control group, using one way analysis of variance “ANOVA” followed by LSD multiple comparisons.

Biochemical parameters	Control group (n = 25)	Patients (n = 100)		P1	P2
		Preoperative	Post-operative		
Active Leptin “ng/ml”	7.78 ± 2.22	32.48 ± 8.59	32.26 ± 7.50	0.000**	0.645 NS
Homocysteine, “μmol/L”	9.17 ± 1.24	14.04 ± 1.58	13.3 ± 1.56	0.000**	0.000**
Galectin-3, “ng/ml”	5.48 ± 1.68	25.96 ± 8.06	23.79 ± 7.95	0.000**	0.001**
Total phospholipids, “g/l”	8.42 ± 1.64	2.47 ± 0.72	2.7 ± 0.76	0.000**	0.006**

P1= Control versus Preoperative.
P2= Preoperative versus Postoperative.
*Indicate significant change at $P < 0.05$; ** indicate significant change at $p < 0.01$; *** indicate significant change at $p < 0.001$. NS means non significant ($p > 0.05$).

For homocysteine (Hcy), the findings of our study were in agreement with Cavalca et al. [20] and Naureen et al. [21], who found that plasma Hcy concentrations were significantly higher in patients with myocardial infarction than in controls.

Myocardial injury generates inflammatory signals that recruit activated macrophages to the myocardium. Mediators such as osteopontin stimulate these macrophages to secrete galectin-3. Galectin-3 may be particularly important in patients with IHD in whom there is sufficient inflammatory substrate for macrophage recruitment and subsequent galectin-3 secretion [22]. The findings of our study suggest for the first time that circulating galectin-3 levels can be used as a marker for chronic IHD as its serum levels were significantly higher among patients with chronic cardiac ischemia when compared with the control group, although it is more valuable diagnostic and prognostic biomarker in heart failure patients. The use of galectin-3 as a marker of chronic cardiac ischemia needs further assessments.

For total phospholipids, our findings were in agreement with Papathanasiou et al. [23]. Also a study by Nagao et al. [24], who reported a significant decrease in the amounts of total phospholipids in the mitochondrial fractions prepared from ischemic myocardial in an ischemic myocardial model, suggesting that disturbances in phospholipid metabolism may be one of the critical alterations that produce irreversible injury during ischemia.

Interestingly, activation of hexosamine biosynthesis pathway (HBP) and increase in the level of O-linked-N-acetylglucosamine (O-GlcNAc) on serine and threonine residues of cytoplasmic and nuclear proteins (which represent bounded form of hexosamines), have been associated with increased tolerance of cells to stress [25], and some studies have suggested it might be also associated with ischemic cardioprotection [26]. Regarding hexsoamines serum levels, the findings of our study revealed significant lower serum total and bound hexosamines levels preoperatively when compared with the control group ($p < 0.01$), which indicate that total and bound hexosamines (in the form of glycoproteins and proteoglycans) play an important role in protection against cardiac ischemia. At the same time there were significant higher serum free hexosamines and free to bound hexosamines ratio preoperatively when compared with the control group ($p < 0.01$), which indicate that free hexosamines in the form of glucosamines and galactosamines are implicated in the pathogenesis of cardiac ischemia.

Table 4
Comparison of the serum levels of hexosamines (total, free, bound, free to bound ratio) preoperative and postoperative versus the control group, using one way analysis of variance “ANOVA” followed by LSD multiple comparisons.

Biochemical parameters	Control group (n = 25)	Patients (n = 100)		P1	P2
		Preoperative	Post-operative		
Hexosamines (total), mg/dl	90.3 ± 24.5	58.3 ± 7.4	60.4 ± 7.633	<0.001**	0.002**
Hexsoamines (free), mg/dl	0.796 ± 0.2	1.6 ± 0.7	0.765 ± 0.21	<0.001**	<0.001**
Hexosamines (bound), mg/dl	89.5 ± 24.5	56.7 ± 7.5	59.67 ± 7.5	<0.001**	<0.001**
Free to bound hexosamines ratio	0.009 ± 0.003	0.03 ± 0.016	0.013 ± 0.003	<0.001**	<0.001**

P1= Control versus Preoperative.
P2= Preoperative versus Postoperative.
*Indicate significant change at $P < 0.05$; ** indicate significant change at $p < 0.01$; *** indicate significant change at $p < 0.001$. NS means non significant (($p > 0.05$).

To the best of our knowledge, no previous studies could be traced in literature regarding the effect of CABG on the serum levels of the ischemic biochemical parameters that have been measured in the present study, except for homocysteine. The present study revealed significant lowering in the serum levels of galectin-3, free hexosamines and free to bound hexosamines ratio and significant increasing in the serum levels of total phospholipids, total and bound hexosamines ($p < 0.01$ for each) following CABG when compared with the preoperative serum levels but still not reaching the serum levels of the control. Regarding the serum levels of homocysteine following CABG, the present study revealed significantly lower levels when compared with the preoperative levels ($p < 0.01$). In agreement with these findings, Parvizi et al. [27] who noticed a marked postoperative reduction of the plasma homocysteine levels in patients undergoing CABG.

The findings of the present study revealed no significant postoperative changes in the serum level of active leptin. Khafaji et al. [17] reported that no difference in the serum leptin between patients with acute myocardial infarction who achieved coronary reperfusion using thrombolytic therapy versus those who don't achieve reperfusion, suggesting that leptin is not released from the myocytes and concluding that serum leptin levels cannot be used as predictors for coronary reperfusion.

4.1. Study limitations

These limitations include the small number of the included patients and short post-operative follow up, so repeated measurements of such ischemic biomarkers 3−6 months post-CABG to confirm the present findings on a larger-scale studies is recommended.

5. Conclusions

The findings of this study revealed significant hemodynamic changes regarding the heart rate, arterial blood pressure and central venous pressure in patients undergoing CABG. Also, these findings prove that high active leptin, homocysteine, galectin-3, free and free to bound hexosamines ratio and low total phospholipids, total and bound hexosamines play an important role in the pathogenesis of myocardial ischemia. The serum levels of homocysteine, galectin-3, hexosamines and total phospholipids, but not active leptin are significantly changed following CABG, so their serum levels may be used as predictors for coronary reperfusion.

Ethical approval

The Research Committee at Faculty of Medicine, Assiut University approved this study (R. Nr. 17/02/016).

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none.

Conflicts of interest

None.

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