Changes in omentin levels and its mRNA expression in epicardial adipose tissue in patients undergoing elective cardiac surgery: the influence of type 2 diabetes and coronary heart disease

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Short title: Omentin in cardiac surgery

Abstract

Omentin is a protein produced by numerous tissues including adipose tissue. Its concentrations are decreased in patients with obesity, type 2 diabetes mellitus (DM) and coronary artery disease (CAD). Experimental studies suggest that omentin may have anti-inflammatory and insulin-sensitizing properties. In the present study, we measured circulating omentin levels and its mRNA expression in epicardial and subcutaneous fat, intercostal and heart muscle before and after elective cardiac surgery in patients with CAD (CAD+, DM-, n=18), combination of CAD and DM (CAD+, DM+, n=9) or with none of these conditions (CAD-, DM-, n=11). The groups did not differ in baseline anthropometric and biochemical characteristics with the exception of higher blood glucose and HBA_{1c} in CAD+, DM+ group.

Baseline circulating omentin levels tended to be lower in CAD+, DM- and CAD+, DM+ groups as compared to CAD-, DM- group and cardiac surgery increased its concentration only in CAD-, DM- group. The change in serum omentin levels during surgery inversely correlated with epicardial fat thickness. While baseline omentin mRNA expression did not differ among the groups in any of the studied tissues, its increase after surgery was present only in subcutaneous fat in CAD-, DM- and CAD+, DM- groups, but not in CAD+, DM+ group. Intercostal muscle omentin mRNA expression increased after surgery only in CAD-, DM- group. In conclusion, cardiac surgery differentially affects omentin levels and subcutaneous fat and skeletal muscle mRNA expression in patients without coronary artery disease and diabetes as compared to patients with these conditions.

Key words

Omentin, Epicardial fat, Type 2 diabetes mellitus, Coronary artery disease, Cardiac surgery

Introduction

Disturbed endocrine function of adipose tissue plays a major role in the development of metabolic complications of obesity, in particular DM, and contributes to the initiation of subclinical inflammation and increased risk of cardiovascular complications in obese patients (Bluher 2013). Obesity is typically accompanied by increased adipose tissue production of pro-inflammatory adipokines and cytokines such as leptin, resistin, TNF-alpha and decreased production of insulin-sensitizing factors such as adiponectin (Baldasseroni *et al.* 2012; Cao 2014). Modulation of endocrine function of adipose tissue could represent a novel possibility of prevention and/or treatment of obesity-related complications. This is why there is an ongoing interest in search for novel adipose tissue-derived factors with metabolically positive anti-inflammatory properties.

Within different adipose tissue depots, epicardial fat represents a unique depot anatomically closely related to heart and believed to affect myocardium metabolism and development of coronary atherosclerosis and other heart diseases (Iacobellis and Barbaro 2008; Matloch *et al.* 2018; Matloch *et al.* 2016). Studies suggest that local production of adipokines, cytokines and other factors in epicardial fat may play an important role in the development of obesity- and diabetes-related heart diseases (Mazurek *et al.* 2003; Kremen *et al.* 2006; Kotulak *et al.* 2014; Kotulak *et al.* 2011).

Omentin is a hydrophilic protein with a molecular weight of 35 kDA originally identified in an omental fat cDNA library and described in intestinal Panneth cells (Komiya *et al.* 1998)

and stromal vascular cells predominantly in omental adipose tissue (Yang *et al.* 2006). Its expression was described also in other cells and tissues including endothelial cells, epicardial fat, small intestine, thymus, lungs or placenta (Tan *et al.* 2015). Omentin is encoded by two genes: omentin 1 and omentin 2 with omentin 1 being the major circulating form (Tan *et al.* 2010). In this study, we focused specifically on omentin 1 and refer to it as omentin throughout the paper.

Omentin is released into circulation and its levels are decreased in patients suffering from obesity and its metabolic complications (de Souza Batista *et al.* 2007; Auguet *et al.* 2011). Lower circulating levels of omentin were associated with glucose intolerance, elevated blood pressure, dyslipidemia and increased waist circumference (Shibata *et al.* 2012). Circulating omentin levels predicted cardiovascular events independently from the presence and extent of angiographically determined baseline CAD (Saely *et al.* 2016) and were used as a predictor of cardiovascular events in patients with CAD (Saely *et al.* 2016). Interestingly, systemic administration of human omentin in mice reduced infarct size after I/R injury via phosphorylation of AMP-activated protein kinase and Akt-dependent mechanisms (Kataoka *et al.* 2014) suggesting a possible direct role of omentin in the regulation of myocardial metabolism.

In the present study, we measured circulating omentin levels and its mRNA expression in epicardial and subcutaneous fat and intercostal and heart muscle before and after elective cardiac surgery in patients with coronary artery disease, combination of coronary artery disease and type 2 diabetes mellitus or with none of these conditions. We hypothesized that the combination of CAD and DM will result in further decrease in omentin concentrations. We also expected a universal role of omentin in postoperative inflammatory response regardless of the presence of CAD or DM.

Methods

Study subjects

The study included 38 patients who underwent elective cardiac surgery with cardiopulmonary bypass (coronary artery by-pass graft (CABG) – 13 subjects, valve replacement – 18 subjects, combination of CABG and valve replacement – 7 subjects). Subjects were divided into 3 groups according to the presence of CAD and DM – 11 subjects without CAD and DM (CAD-, DM- group), 18 subjects with CAD and without DM (CAD+, DM- group) and 9 subjects with CAD and DM (CAD+ and DM+ group). Patients with diabetes (n=9) were treated with metformin (4 patients), **sulfonylureas** (1 patient), DPP4 inhibitors (2 patients), insulin (1 patient) or diet only (1 patient). Thirty-three of participating patients had arterial hypertension and 32 dyslipidemia treated by statins. None of the patients suffered from acute or chronic kidney disease, malignancy, thyroid disease, or acute infection.

Surgery was performed after overnight fasting and was started between 7-8 AM in all subjects. Ten patients received infusion of dobutamine and norepinephrine perioperatively with maximum dose of 7 μg/kg/min and 0.2 μg/kg/min, respectively with treatment duration from 8 to 33 h.

All participants signed written informed consent prior to the enrollment into the study. The study was approved by Human Ethics Review Board, First Faculty of Medicine and General University Hospital, Prague, Czech Republic and was performed in accordance with the guidelines proposed in Declaration of Helsinki (2000) of the World Medical Association.

Anthropometric examination, blood and tissue sampling

Anthropometric examination of study subjects was performed at baseline one day prior to operation. All subjects were measured and weighted and their BMI was calculated. Waist and hip circumference were measured. Blood samples for hormonal and biochemical measurements were taken prior to initiation of anesthesia (baseline) and at the end of the operation. Serum was obtained by centrifugation and samples were subsequently stored in aliquots at − 80 °C until further analysis. Samples of subcutaneous (thoracic region, sternotomy site) (SAT) and visceral (epicardial) adipose tissue (EAT), intercostal muscle (ICM) and myocardial right atrium (RA) for mRNA expression analysis were taken at the start and prior to the end of the surgery from approximately the same location in all patients. Tissue samples were collected to 1 ml of RNAlater® reagent (Ambion® - Invitrogen, Carlsbad, California, USA) and stored at − 80 °C until further analysis. The thickness of EAT was measured by transthoracic echocardiography in front of the right ventricular wall from the parasternal long axis (PLAX) view.

Hormonal and biochemical assays

Serum levels of omentin were measured using ELISA kit (BioVendor, Modrice, Czech Republic) with a limit of detection 0.5 ng/ml. Serum C-reactive protein (CRP) levels were measured by high sensitive assay (Bender Med systems, Vienna, Austria) with a sensitivity of 3 pg/ml. Insulin levels were measured by RIA kit (Cis Bio International, Gif-sur-Yvette, France). Sensitivity was 2.0 µIU/ml. The intra- and inter-assay variability of the kits was less than 5 % and less than 10 %, respectively.

Routine biochemical parameters were measured at the Department of Biochemistry, General University Hospital, Prague, Czech Republic by standard laboratory methods. LDL

cholesterol was calculated using Friedewald Equation. The homeostasis model assessment (HOMA) was calculated as HOMA-IR index using the following formula: fasting serum insulin (mIU/l) x fasting serum glucose (mmol/l)/22.5.

Quantitative real-time PCR

mRNA expression of omentin was determined as described in detail elsewhere (Dolezalova *et al.* 2007). Briefly, samples of tissue were homogenized on MagNA Lyser Instrument (Roche Diagnostics GmbH, Mannheim, Germany). Total RNA was extracted on MagNA Pure instrument using Magna Pure Compact RNA Isolation kit (Roche Diagnostics GmbH, Mannheim, Germany). Reverse transcription was performed using random primers according to the manufacturer's protocol of the High-Capacity cDNA Reverse Transcription Kits (Applied Biosystems, Foster City, CA, USA).

Gene expression analysis was performed on a 7500 Real-Time PCR System using TaqMan® gene Expression Assays (Applied Biosystems, Foster City, CA, USA). For reaction, a mix of TaqMan® Universal PCR Master Mix II, NO AmpErase® UNG (Applied Biosystems, Foster City, CA, USA) and specific TaqMan® Gene expression Assays (Applied Biosystems, Foster City, CA, USA) were used. Beta-2 microglobulin (B2M) was used as endogenous reference. The formula 2^{-ddCt} was used to calculate relative gene expression.

Statistical analysis

Statistical analysis was performed. Graphs were drawn using SigmaPlot 13.0 software (SPSS Inc., Chicago, IL, USA). The results are expressed as mean ± standard error (SD) or median (interquartile range). Normality of all data was assessed by using of the Shapiro-Wilk test.

One-way ANOVA followed by Holm-Sidak test or One-way ANOVA on Ranks followed by Dunn's method and paired t-test or Wilcoxon Signed-Rank test were used for the assessment of intra and intergroup differences, as appropriate. Correlations were analyzed using Spearman's or Pearson's correlation test, according to the normality of data. Multiple linear regression analysis using backward stepwise variable selection method was performed in the combined group including all study subjects using parameters with significant result from Spearman or Pearson correlation test. In all statistical tests, p values <0.05 were considered significant.

Results

Biochemical, anthropometric and hormonal characteristics of study subjects

There were no differences among the three groups regarding demographic and anthropometric data including age, weight, height, BMI, waist and hip circumference and waist/hip ratio (Tab. 1). However, the thickness of epicardial fat was significantly higher in CAD+, DM+ group as compared to CAD-, DM- group.

As expected, baseline HbA_{1c} and glucose levels were higher in CAD+, DM+ group as compared to other groups, while showing no difference between CAD-, DM- group and CAD+, DM- group. HOMA-IR index was higher in CAD+, DM+ group as compared to CAD-, DM- group, whereas it did not differ between CAD-, DM- group and CAD+, DM- group (Tab. 1).

Baseline biochemical parameters including lipid panel, renal parameters and liver tests did not differ between the groups and were not affected by surgery (data not shown).

Effect of surgery on blood glucose, serum insulin and C-peptide

Cardiac surgery significantly increased glucose levels relative to baseline in all groups. At the end of the operation, glucose levels were higher in CAD+, DM+ group as compared to other groups. C-peptide levels increased at the end of operation relative to baseline in both no CAD+, DM- and CAD+, DM- groups while being unaffected in CAD+, DM+ group. Insulin levels were not changed by surgery (Tab. 2).

Effect of cardiac surgery on serum omentin levels and mRNA expression in adipose, skeletal muscle and heart tissue

Baseline omentin levels tended to be higher in CAD-, DM- group (Table 2). At the end of operation serum omentin increased significantly in CAD-, DM- group relative to baseline, while no change was detected in either CAD+, DM- group or CAD+, DM+ group. Serum omentin concentrations at the end of operation in CAD+, DM- group were lower as compared to CAD-, DM- group (Figure 1).

Baseline omentin mRNA expression did not statistically significantly differ in any group in either subcutaneous or epicardial fat or skeletal muscle and heart tissue, even though a marked trend to higher values was observed in EAT of both CAD+, DM- and CAD+, DM+ groups as compared to CAD-, DM- as well as to corresponding SAT (Figure 2a, 2b). Cardiac surgery significantly increased omentin mRNA expression in subcutaneous adipose tissue and skeletal muscle in CAD-, DM- and CAD+, DM- groups and in skeletal muscle of CAD-, DM- group, while no effect was seen in CAD+, DM+ group. Omentin mRNA expression in epicardial fat tended to decrease after surgery in CAD+, DM- and CAD+, DM+ groups while showing an opposite tendency in CAD-, DM- group; however, none of the differences reached statistical significance owing to the heterogeneity of results. As compared to baseline, postoperative

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omentin mRNA expression in the right atrial tissue significantly decreased in CAD+, DM-group while it was not affected either in CAD-, DM- group or CAD+, DM+ group.

The relationship of omentin with other studied parameters

The relationship of serum omentin levels and mRNA expression with anthropometric, biochemical, and hormonal parameters was studied in a combined population of all 3 study groups. The only correlation identified was a weak inverse relationship with serum creatinine ($p = 0.030$, $R = -0.254$).

No relationship between omentin mRNA expression and anthropometric, biochemical and hormonal characteristics was found at baseline or after surgery.

Change in serum omentin levels (difference between baseline and end-of-surgery omentin) inversely correlated with epicardial fat thickness ($p = 0.016$, $R = -0.396$), HDL cholesterol ($p = 0.046$, $R = -0.335$) and leptin levels before ($p = 0.020$, $R = -0.382$) and after surgery ($p = 0.032$, $R = -0.358$). Backward stepwise regression analysis demonstrated that difference between baseline and end of the surgery omentin could be independently predicted only from serum leptin concentration after surgery ($p = 0.029$; $\beta = -0.341$) and HDL cholesterol ($p = 0.014$; $\beta = -0.387$). The adjusted Adj R^2 was 0.271 for the whole analysis.

Discussion

Endocrine function of adipose tissue is markedly affected by the presence of obesity or type 2 diabetes mellitus with increased production of pro-inflammatory and decreased production of anti-inflammatory factors relative to healthy subjects (Bluher 2013; Luo and Liu 2016). This

endocrine dysfunction subsequently contributes to the development of metabolic and cardiovascular complications of obesity (Bluher 2013; Bluher 2012). Modulation of endocrine function of adipose tissue may thus represent a potential therapeutic target to prevent or treat these complications.

Omentin is one of the few anti-inflammatory adipokines with possible protective function against obesity-induced metabolic and cardiovascular complications (Tan *et al.* 2015). Its serum concentrations are decreased in patients with obesity and type 2 diabetes mellitus and increase after weight reduction induced by bariatric surgery (Urbanova *et al.* 2014). It has been previously documented that omentin has an inhibitory effect on TNF-induced vascular inflammation in human endothelial cells (Yamawaki *et al.* 2011) and induces vasodilation in isolated rat blood vessels (Yamawaki *et al.* 2010). Furthermore, omentin treatment of epicardial fat improved its anti-inflammatory activity and insulin sensitivity (Fernandez-Trasancos *et al.* 2017).

Our study focused on the two hitherto unexplored questions with respect to a possible relationship of omentin and cardiovascular complications: the changes of systemic omentin levels after cardiac surgery and the changes of omentin mRNA expression in epicardial and subcutaneous fat along with skeletal and heart muscle after cardiac surgery. We found a tendency towards lower circulating omentin concentrations in patients with either coronary artery disease alone or its combination with type 2 diabetes as compared to the group with none of these diseases. Previous studies have documented decreased omentin levels in patients with CAD relative to subjects without CAD (Du *et al.* 2016; Onur *et al.* 2014). The reason for the lack of significant changes in omentin levels in our study may lie in the relatively small groups and slightly different patient characteristics (e.g. ethnic differences) as compared to some of previous studies**. Also, our results may have been influenced by the fact that we have included patients of both genders (although majority of patients were**

men) and some studies suggested that omentin levels may be affected by gender (*Luque-RamIrez et al,* 2013). Nevertheless, the direction of differences in omentin levels between patients with and without CAD in our study was the same as in previously published data.

One of the most interesting findings of our study was the increase in omentin levels after cardiac surgery that was present only in patients without coronary artery disease or diabetes while no such change was observed in patients with either CAD alone or CAD+, DM+. It is tempting to speculate that this increase may represent a protective mechanism that helps the myocardium overcome the surgery-induced inflammatory and stress response. Such reaction appears to be present only in "healthier" patients without CAD or DM. This hypothesis is further supported by the correlation analysis in our study showing an inverse relationship between the change in serum omentin levels during surgery and epicardial fat thickness. Increased thickness of epicardial fat is a well-documented risk factor for cardiovascular diseases including coronary artery disease (Ahn *et al.* 2008), sudden death from stable coronary artery disease (Fuller *et al.* 2017) and endothelial dysfunction (Aslan *et al.* 2015). In our study, the epicardial fat thickness was significantly higher in CAD+, DM+ group that showed no response of omentin levels to cardiac surgery.

The changes in circulating omentin levels in patients with CAD-, DM- – i.e. the healthiest group of patients – were paralleled by increases in omentin mRNA expression in subcutaneous fat and intercostal muscle. None of these changes was detectable in CAD+, DM+ group arguing again for differential regulation of omentin production in subjects with both metabolic dysfunction and coronary heart disease. This concept was further supported by the trend to increased omentin mRNA expression in EAT of CAD+, DM+ and CAD+, DM- subjects as compared with CAD-, DM- group as well as with corresponding SAT. These findings are in accordance with the data by Fain et al. who showed markedly higher omentin mRNA expression in epicardial as compared with subcutaneous fat (Fain *et al.* 2008).

A direct comparison of EAT omentin mRNA expression between subjects with and without CAD has thus far been performed in 2 studies on East Asian populations with opposite results alleged to differences in study populations including anthropometric parameters and the prevalence of diabetes mellitus (Du *et al.* 2016; Harada *et al.* 2016). Our data on a Caucasian population confirm the findings by Harada et al. who showed increased omentin mRNA expression in EAT of subjects with CAD (Harada *et al.* 2016). Furthermore, this trend was in our study persisting regardless of the presence of diabetes mellitus and a tendency to increased body weight in the CAD+, DM+ group suggesting a potential compensatory protective role of epicardial omentin in coronary artery disease.

Previous human studies focused exclusively on omentin mRNA expression in fat (Watanabe *et al.* 2017; Katsi *et al.* 2014). Our study is the first one to measure omentin mRNA expression in parallel in both epicardial and subcutaneous fat and myocardial and intercostal muscle. The first interesting observation from these data was a significant increase in intercostal muscle omentin mRNA expression in CAD-, DM- group only as compared to tendencies towards decreased omentin expression in CAD+, DM- and CAD+, DM+ groups. These finding suggest a possibility that skeletal muscle could serve as a significant source of omentin and that its production may be modulated by the metabolic status of the patients and the presence or absence of cardiovascular complications, respectively. In contrast, omentin mRNA expression in the samples obtained from myocardial right atrium tended to decrease at the end of operation and this decrease reached statistical significance only in CAD+, DM- group.

Taken together our study has shown that serum omentin levels are significantly increased after cardiac surgery in patients without type 2 diabetes and coronary artery disease while no such changes are detectable in patients with coronary artery disease alone or its combination with type 2 diabetes. Similar findings were observed on the mRNA expression level in

intercostal muscle and subcutaneous fat. These data suggest that omentin may be released during cardiac surgery as a protective factor against surgery-induced stress and inflammation in relatively healthy patients but not in those with metabolic and cardiovascular complications. Further studies are necessary to explore these relationships in larger cohorts of patients and to test the possible protective potential of omentin in metabolic and cardiovascular diseases.

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Tab. 1 Anthropometric and biochemical characteristics of study subjects at baseline

Group	CAD-, DM-	CAD+, DM-	CAD+, DM+
No. of subjects	11	18	9
Age (year)	59.8±15.9	67.9±8.76	67.0±8.76
Sex (males/females)	8/3	15/3	7/2
Weight (kg)	80.5±13.2	85.7±16.8	91.8±14.1
Height (cm)	172±10.2	176±7.9	174±8.56
Body mass index (kg/m^2)	27.1±3.17	27.7±5.09	30.4±3.59
Waist circumference (cm)	99.2±11.7	100±13.1	110±8.08
Hip circumference (cm)	102±10.2	105±8.47	111±4.52
Waist/hip ratio	0.97 (0.93-0.99)	0.96 (0.91-1.01)	0.98 (0.93-1.05)
Epicardial adipose tissue thickness (mm)	3.00 (2.00-3.25)	3.00 (3.00-4.00)	5.00 (3.50-6.00)[o]
Fasting glucose (mmol/l)	5.40 (5.00-5.90)	5.80 (5.10-6.50)	8.00 (6.45-9.80)[o, z]
HbA$_{1c}$ (mmol/mol)	35.0 (32.0-38.0)	37.5 (34.0-40.8)	50.0 (44.5-60.0)[o, z]
HOMA-IR index	4.38 (3.70-5.54)	5.66 (3.73-13.35)	9.79 (7.55-10.81)[o]

Normally distributed data are shown as mean ± SD, non-parametric data as median (interquartile range). Statistical significance is from One-way ANOVA; ^{o} p<0.05 vs. CAD-, DM- group, ^{z} p<0.05 vs. CAD+, DM- group. Abbreviations: CAD – coronary artery disease, DM – diabetes mellitus, HbA_{1c} – glycosylated hemoglobin, HOMA-IR index - homeostasis model assessment – insulin resistance; IFCC, International Federation of Clinical Chemistry.

Tab. 2 Effect of elective cardiac surgery on serum glucose and hormonal parameters

Group	CAD-, DM-		CAD+, DM-		CAD+, DM+	
Time	T1	T2	T1	T2	T1	T2
Serum glucose (mmol/l)	5.40 (5.00-5.90)	8.00 (7.40-9.30) *	5.80 (5.10-6.50)	8.50 (7.20-9.50) *	8.00 (6.45-9.80)$^{o, z}$	10.4 (9.10-12.8) *$^{·o·z}$
Serum insulin (mIU/l)	19.1 (14.4-21.9)	26.4 (14.6-65.6)	20.9 (15.3-43.8)	19.2 (13.9-53.3)	26.1 (19.9-30.7)	26.1 (18.6 -98.4)
C-peptide (ng/ml)	2.76±0.95	4.19±2.54*	3.07±1.11	4.24±3.33*	3.13±1.26	2.95±1.11
Leptin (ng/ml)	5.83 (3.54 - 10.2)	3.45 (2.03 - 5.14)*	6.97 (3.89 - 15.2)	3.65 (2.76 - 9.73)*	7.12 (5.41 - 16.0)	5.73 (3.29 - 11.6)*
Omentin (ng/ml)	636±188	774±225*	489±245	527±244 ^{o}	575±253	586±369

Normally distributed data are shown as mean ± SD, non-parametric data as median (interquartile range). Statistical significance is from One-way ANOVA and paired t-test (T1 vs. T2) *p<0.05 vs. T1; ^{o} p<0.05 vs. CAD-, DM- group; ^{z} p<0.05 vs. CAD+, DM- group. Abbreviations: CAD – coronary artery disease, DM – diabetes mellitus; T1 beginning of surgery, T2 end of surgery.
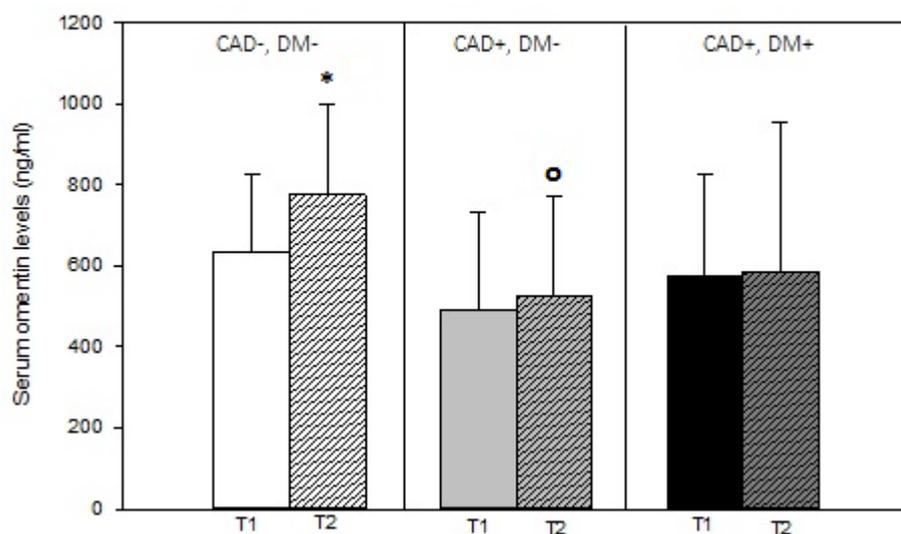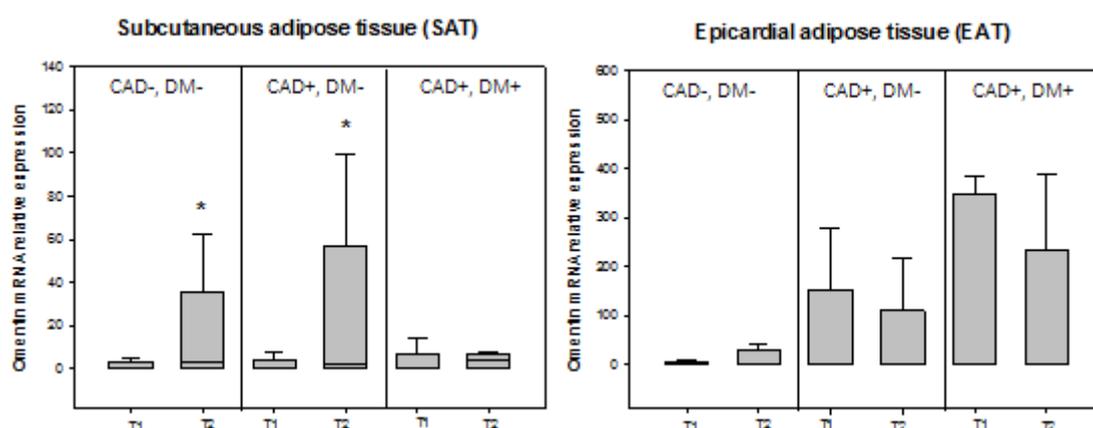
Fig. 1 Serum omentin levels: the effect of elective cardiac surgery. Values are mean ± SD. Statistical significance is from One-way ANOVA and paired t-test (T1 vs. T2) *p<0.05 vs. T1. ° p<0.05 vs. CAD-, DM- group.

Abbreviations: CAD – coronary artery disease, DM – diabetes mellitus; T1 beginning of surgery, T2 end of surgery.

Fig. 2a. Relative gene expression of omentin mRNA in SAT and EAT: the effect of elective cardiac surgery. Values are median and interquartile range. Statistical significance is from One-way ANOVA and paired t-test (T1 vs. T2) *p<0.05 vs. T1.. Abbreviations:
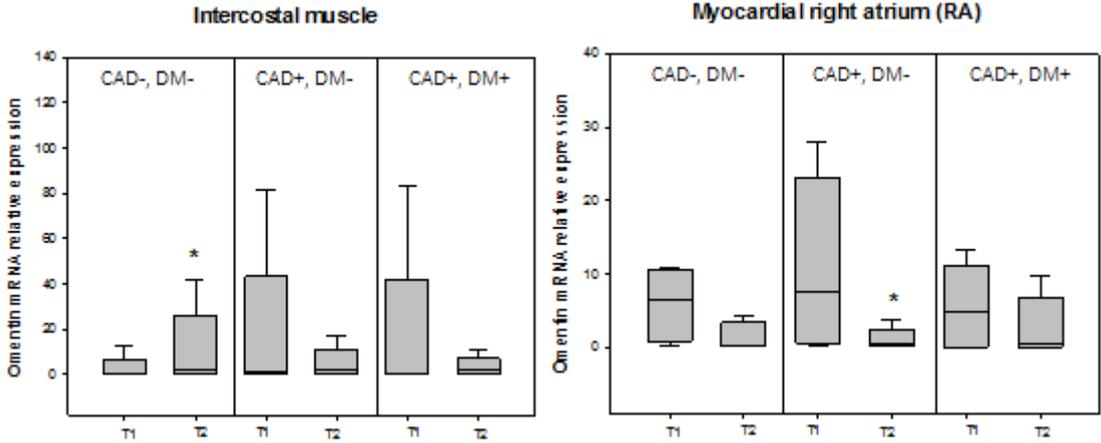
Fig. 2b. Relative gene expression of omentin mRNA in ICM and RA: the effect of elective cardiac surgery. Values are median and interquartile range. Statistical significance is from One-way ANOVA and paired t-test (T1 vs. T2) *$p<0.05$ vs. T1. Abbreviations: CAD – coronary artery disease, DM – diabetes mellitus; T1 beginning of the surgery, T2 end of the surgery.