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ARTICLE

Serum levels of chemerin, apelin, vaspin, and omentin-1 in obese type 2 diabetic Egyptian patients with coronary artery stenosis

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Abstract: Cardiovascular diseases (CVD) are the leading cause of death in the diabetic population. Obesity is a serious problem that has been linked with CVD and diabetes via a variety of adipokines. The aims of this study were to evaluate and correlate circulating chemerin, apelin, vaspin, and omentin-1 levels in obese type 2 diabetic Egyptian patients with coronary artery stenosis (CAS), and to assess their usefulness as noninvasive diagnostic biomarkers. Chemerin, apelin, vaspin, and omentin-1 levels were determined by enzyme immunoassay in coronary artery disease (CAD) I patients (45 non-obese, nondiabetic with CAS), CAD II patients (45 obese, diabetic with CAS), and 30 controls. Patients in CAD I and CAD II groups exhibited higher levels of chemerin and apelin together with lower levels of vaspin and omentin-1 than in controls. These alterations were more significant in CAD II than in CAD I patients. Additionally, adipokine levels were individually correlated with each other and with certain biochemical variables. Moreover, chemerin and vaspin levels could differentiate CAD II patients from CAD I and controls. Alterations of these adipokines may play a crucial role in the pathogenesis of CAS in obese type 2 diabetic Egyptian patients. Chemerin and vaspin could be used as markers to support diagnosis of CAS.

Key words: chemerin, apelin, vaspin, omentin-1, obesity, T2DM, coronary stenosis.

Résumé : Les maladies cardiovasculaires (MCV) sont la principale cause de décès dans la population de patients atteints de diabète. L'obésité est un problème grave que l'on a lié aux MCV et au diabète par l'intermédiaire de diverses adipokines. La présente étude avait pour objectif d'évaluer et de corréler les taux de chémérine, d'apéline, de vaspine et d'omentine 1 en circulation chez des Égyptiens obèses atteints de diabète de type 2 et présentant une sténose coronarienne (SC), ainsi que d'évaluer l'utilité de ces taux comme biomarqueurs diagnostiques non effractifs. Nous avons établi les taux de chémérine, d'apéline, de vaspine et d'omentine-1 à l'aide d'essais immunoenzymatiques chez des patients répartis dans trois groupes : coronaropathie I (45 patients atteints de MCV sans obésité ni diabète), coronaropathie II (45 patients atteints de MCV avec obésité et diabète) et témoin (n = 30). Les patients des groupes coronaropathie I et II présentaient des taux plus élevés de chémérine et d'apéline, avec des taux moins élevés de vaspine et d'omentine-1 que chez les témoins. Ces modifications étaient plus importantes dans le groupe coronaropathie II que dans le groupe coronaropathie I. De plus, les taux d'adipokine étaient individuellement proportionnels les uns aux autres, ainsi qu'à certaines variables biochimiques. En outre, les taux de chémérine et de vaspine permettaient de différencier les patients du groupe coronaropathie II de ceux des groupes coronaropathie I et témoin. La modification du taux de ces adipokines pourrait jouer un rôle crucial dans la pathogenèse de la SC chez les Égyptiens obèses atteints de diabète de type 2. La chémérine et la vaspine pourraient être utilisées comme marqueurs à l'appui du diagnostic de SC. [Traduit par la Rédaction]

Mots-clés : chémérine, apéline, vaspine, omentine 1, obésité, DT2, sténose coronarienne.

Introduction

Cardiovascular diseases (CVD) are the leading global cause of death, accounting for 17.5 million deaths per year, a number that is expected to grow to more than 23.6 million by 2030 (Heart Disease and Stroke Statistics 2017). CVD result mainly from atherosclerosis, which involves a chronic and progressive inflammatory response of the vessel wall to injuries promoted by risk factors such as hypertension, dyslipidemia, diabetes, and others (Libby et al. 2010).

CVD have been considered as the most important cause of death in diabetic patients and diabetes can in turn increase the risk of cardiovascular events (Lima et al. 2015). Type 2 diabetes mellitus (T2DM) is usually preceded with a state of insulin resistance that plays a crucial role in the pathogenesis of the disease (Xu et al. 2015) and its associated complications (Timar et al. 2014).

Obesity is a serious chronic and growing problem of excessive body fat that has been linked with dyslipidemia, CVD, and diabetes (Cordido et al. 2014). White adipose tissue is recognized as an important player in obesity-mediated inflammation and CVD. Indeed, white adipose tissue is an active endocrine organ that contributes to the inflammatory process in obese subjects and secretes a variety of adipokines (Wang and Nakayama 2010). These adipokines including chemerin, vaspin, omentin-1, and apelin affect the whole-body homeostasis by influencing numerous physiological and biological processes (Khan and Joseph 2014) and

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fulfilling their actions via different signaling pathways and chemical mediators (Kang et al. 2016).

Chemerin, a 16 kDa chemoattractant protein, consists of 131–137 amino acids and acts as a ligand for the G-protein coupled receptors CMKLR1 (ChemR23) (Wittamer et al. 2003). It is secreted by white adipose tissue as prochemerin (18 kDa), and is transformed into its active protein by serine protease cleavage of its C-terminal fragment (Zabel et al. 2005). Chemerin is a pro-inflammatory cytokine that recruits and activates immune cells and contributes to inflammation by promoting macrophage adhesion to vascular cell adhesion molecule-1 (VCAM-1) and fibronectin (Ouchi et al. 2011). Moreover, it has been reported that chemerin potentiates insulin-stimulated glucose uptake and enhances insulin signaling in 3T3-L1 adipocytes (Takahashi et al. 2008).

Another adipokine is apelin, an endogenous ligand for the orphan G-protein coupled receptor (Schilffarth et al. 2009) that has been shown to enhance insulin sensitivity and delay the development of metabolic disorders associated with obesity (Dray et al. 2010). Furthermore, it has been suggested that apelin plays a role in angiogenesis and collateral vessel formation (Momiyama 2014), and has been presented as a novel biomarker for predicting T2DM (Ma et al. 2014).

Vaspin (visceral adipose tissue–derived serine protease inhibitor) is a unique insulin-sensitizing adipokine that has been demonstrated to improve glucose tolerance and insulin resistance in obese mice (Hida et al. 2005). Moreover, a strong relation was recognized between visceral vaspin expression in humans and their body mass index, body fat percentage, and plasma glucose level (Seeger et al. 2008). Human vaspin is a 45 kDa protein, made of 395 amino acids and exhibits about 40% homology with α-1 anti-trypsin (Hida et al. 2005). The effects of vaspin on vascular cells are thought to be mediated via inhibiting inflammatory factors secretion from vascular smooth muscle cells, and antagonizing endothelial cell apoptosis induced by free fatty acid (Zhang et al. 2013).

Omentin-1, also referred to as intelectin-1, is an adipocytokine composed of 313 amino acids expressed mainly in visceral adipose tissue (Schaffler et al. 2005). Omentin-1, the major isoform in human plasma, is another adipokine with insulin-sensitizing effects (Tan et al. 2010). Additionally, it has been reported to exhibit potential anti-inflammatory effects and to act as a modulator of vascular function (Katsi et al. 2014). Indeed, omentin-1 was included among the good adipokines (Yamawaki et al. 2011).

According to the World Health Organization data published in May 2014 (LeDuc Media 2014), CVD and T2DM deaths in Egypt reached 23.14% and 1.55%, respectively, of total deaths. Furthermore, it is estimated that 70% of Egypt's adult population suffers from obesity, a statistic that places it as the 7th most obese country worldwide. In this context, we hypothesized that circulating levels of the 4 aforementioned adipokines may differ between obese type 2 diabetic Egyptian patients with coronary artery stenosis (CAS) and healthy controls because such patients have increased fat mass, altered insulin resistance, and altered inflammatory milieu. Therefore, this study was designed to evaluate serum levels of chemerin, apelin, vaspin, and omentin-1 in obese type 2 diabetic Egyptian patients with CAS. The study also aimed at investigating the possible correlations between the 4 adipokines and the clinical and biochemical characteristics of those patients. Additionally, the potential usefulness of these adipokines as non-invasive diagnostic biomarkers for CAS was also assessed.

Materials and methods

Subjects

A total of 120 Egyptian participants (48 men and 72 women) aged 45–65 were enrolled in the study: 90 patients with CAS and 30 healthy control subjects. They were medically evaluated by physicians, who took full medical history and conducted physical examination. All participants gave their informed consent and the study was conducted in compliance with the approval of the Research Ethics Committee for Experimental and Clinical Studies at Faculty of Pharmacy, Cairo University, Cairo, Egypt, and according to the Declaration of Helsinki Principles. Patients were recruited from admitted patients to the Intensive Care Unit, Cardiology Department, Kasr El-Einy Hospital, Cairo University, from January to August 2015. Patients with CAS were diagnosed according to typical clinical symptoms and assessment of coronary arteries using conventional coronary angiography, which indicated the presence of more than 50% stable static luminal narrowing caused by atherosclerosis in at least one major coronary vessel. Patients with stable coronary stenosis due to familial hypercholesterolemia and vasculitis and patients with coronary fistula were not included in the study. In addition, patients with CAS who were suffering from type 1 diabetes, renal or hepatic diseases, inflammatory or infectious diseases, endocrine disorders, malignancies, and autoimmune diseases, as well as pregnant and lactating women, were excluded from the study.

Patients with CAS were further classified into 2 groups: coronary artery disease (CAD) I included 45 non-obese, nondiabetic patients with CAS; and CAD II included 45 obese, type 2 diabetic patients with CAS. Diabetic patients had fasting plasma glucose (FPG) ≥126 mg/dL and glycosylated hemoglobin A1c (HbA1c) ≥ 6.5% (International Diabetes Federation 2013). Obese patients were selected to have body mass index (BMI) within a specific range (30 kg/m^2 ≤ BMI < 35 kg/m^2). Control subjects were individuals who came to the hospital for a health examination or for blood donation. They had FPG ≤ 100 mg/dL, HbA1c <6.0%, BMI 20–25 kg/m^2, had a negative history for CAS, and were not suffering any health problems.

Biochemical assays

Fasting venous blood was obtained from all participants; aliquots were collected on EDTA for estimation of FPG (Keilin and Hartree 1948) and HbA1c (Abraham et al. 1978) levels using standard laboratory kits (Stanbio, Texas, USA). Other aliquots of blood were collected in serum separation tubes for determination of the 4 adipokines. Serum apelin (Lee et al. 2000), vaspin (Hida et al. 2005), and omentin-1 (de Souza Batista et al. 2007) levels were estimated using ELISA kit (RayBio Human Kit; RayBiotech, Norcross, Georgia, USA) with inter-assay CV < 15% and intra-assay CV < 10%. The minimum detectable concentrations of the adipokines were for apelin = 5.84 pg/mL, for vaspin = 26.2 pg/mL, and for omentin-1 < 1 ng/mL. Meanwhile, chemerin (Zabel et al. 2008) was estimated using ELISA kit (Boster's Human/Chemerin Kit; Boster Biological Technology Co., Ltd., Pleasanton, California, USA) with inter-assay CV≤8% and intra-assay CV≤5.6% and sensitivity or the minimum detectable concentration of chemerin < 20 pg/mL.

Total cholesterol (TC) (Allain et al. 1974), triacylglycerol (TAG) (Bucolo and David 1973), high-density lipoprotein cholesterol (HDL-C) (Burtis and Ashwood 1999), creatinine, and urea were assessed using standard laboratory kits (Spinreact, Spain). Very low density lipoprotein cholesterol (VLDL-C) and low-density lipoprotein cholesterol (LDL-C) were calculated using the Friedewald equation (Friedewald et al. 1972).

Statistical analysis

The data were computed and statistically analyzed using SPSS statistical software version 20 (SPSS Inc., Chicago, Illinois, USA). The quantitative results were expressed as mean ± standard deviation (SD). Normally distributed parameters were compared using analysis of variance (ANOVA) followed by post hoc Bonferroni test. Non-normally distributed data were further analyzed by Kruskal–Wallis and Mann–Whitney *U* tests. Spearman's rank correlation coefficient and multiple linear stepwise regression analyses were performed to evaluate the association between the 4 adipokines and the clinical and biochemical characteristics of the study par-

Table 1. Clinical and biochemical characteristics of the study participants.

Parameters	Control group (n = 30)	CAD I group (n = 45)	CAD II group (n = 45)
Sex (M/F)	14/16	23/22	11/34
Age (years)	54.6±3.1	53.7±7.6	55.3±6
BMI (kg/m²)	21.8±1.3	23.1±1.8	32.5±1.8*†
SBP (mm Hg)	109±4.1	131.7±10.1*	143.2±12*†
DBP (mm Hg)	74.1±3.8	84±5.9*	86±5.4*
FPG (mmol/L)	4.1±0.35	4.14±0.42	18.7±0.5*†
HbA1c (%)	5.2±0.6	5.4±0.5	8.5±1.5*†
TC (mg/dL)	131.5±13.3	229±37*	261±30.7*†
TAG (mg/dL)	76.7±10.3	213±56*	236±73.5*
HDL-C (mg/dL)	47.8±4.7	45.7±4.5	28±3.7*†
LDL-C (mg/dL)	68±2.67	134.7±6.4*	186.2±22.2*†
VLDL (mg/dL)	15.3±2.2	42.7±14*	47.3±14.1*
TC/HDL-C	2.8±0.4	5.1±0.9*	9.3±0.95*†
LDL-C/HDL-C	1.44±0.07	4.12±0.9*	6.7±1.12*†
Cr (mg/dL)	0.86±0.09	0.77±0.19	0.85±0.31
Urea (mg/dL)	32.8±3.7	36.8±15.6	35.2±15.4

Note: Data are expressed as mean ± SD. CAD, Coronary artery disease; M, male; F, female; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; TC, total cholesterol; TAG, triacylglycerols; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low density lipoprotein; TC/HDL-C, risk factor-1; LDL-C/HDL-C, risk factor-2; Cr, creatinine.

*Significant difference from control group (P < 0.05).

†Significant difference from CAD I group (P < 0.05).

ticipants. P values < 0.05 were considered statistically significant. Receiver operating characteristic curve analysis was used to detect the cut-off value, sensitivity, and specificity of the adipokines.

Results

Clinical and biochemical characteristics of the study participants

As shown in Table 1, CAD I patients showed significantly higher SBP, DBP, TC, TAG, LDL-C, VLDL-C, and atherosclerotic risk ratios compared with normal subjects. Meanwhile, compared with normal healthy individuals and CAD I patients, CAD II patients had significantly higher conventional risk factors for obesity and diabetes complications including BMI, SBP, FPG, HbA1c, TC, TAG, LDL-C, VLDL-C, TC/HDL-C, and LDL-C/HDL-C. On the other hand, HDL-C was significantly lower in CAD II group than both normal and CAD I groups. No significant differences were observed in gender, age, urea, and creatinine between the control group and the other 2 groups.

Serum levels of chemerin, apelin, vaspin, and omentin-1 in different study groups

Results presented in Table 2 indicated that serum levels of chemerin and apelin were significantly higher in both CAD I and CAD II groups compared with normal control group. Additionally, CAD II patients showed significantly higher levels of both adipokines compared with CAD I patients (reaching 183% and 176.7% of the CAD I values, respectively). On the other hand, serum levels of vaspin and omentin-1 were significantly lower in CAD I and CAD II patients compared with normal controls. Additionally, patients in CAD II group exhibited significantly lower values for vaspin and omentin-1 to reach 59.3% and 73% of the values of CAD I group, respectively.

Correlation analyses of chemerin and apelin with the clinical and biochemical characteristics of the study participants

Spearman's correlation analysis revealed significant positive correlations between serum levels of chemerin and BMI, FBG, HbA1c, TC, TAG, LDL-C, VLDL-C, TC/HDL-C, and LDL-C/HDL-C, and a negative correlation with HDL-C in CAD II group (Table 3). Meanwhile, no significant correlation was observed between serum chemerin levels and the clinical and biochemical characteristics of the study participants in CAD I group.

Table 2. Serum levels of chemerin, vaspin, apelin, and omentin-1 in different study groups.

Parameters	Control group (n = 30)	CAD I group (n = 45)	CAD II group (n = 45)
Chemerin (ng/mL)	0.98±0.29	2.015±0.36*	3.7±0.84*†
Apelin (ng/mL)	0.96±0.48	2.15±0.15*	3.8±0.36*†
Vaspin (ng/mL)	0.45±0.12	0.27±0.1*	0.16±0.03*†
Omentin-1 (ng/mL)	0.54±0.12	0.264±0.085*	0.19±0.05*†

Note: Data are expressed as mean ± SD. CAD, Coronary artery disease.

*Significant difference from control group (P < 0.05).

†Significant difference from CAD I group (P < 0.05).

Table 3. Correlation analyses of chemerin and apelin with the clinical and biochemical characteristics of the study participants.

	Chemerin (ng/mL)				Apelin (ng/mL)			
	CAD I		CAD II		CAD I		CAD II	
	r	P	r	P	r	P	r	P
Age (years)	−0.13	NS	−0.06	NS	0.102	NS	0.12	NS
BMI (kg/m²)	0.047	NS	0.89	<0.001	0.098	NS	0.82	<0.001
SBP (mm Hg)	−0.11	NS	0.11	NS	−0.054	NS	0.03	NS
DBP (mm Hg)	0.43	NS	0.05	NS	−0.02	NS	−0.28	NS
FPG (mmol/L)	−0.03	NS	0.76	<0.001	−0.19	NS	0.77	<0.001
HbA_{1c} (%)	0.19	NS	0.81	<0.001	0.094	NS	0.84	<0.001
TC (mg/dL)	0.23	NS	0.86	<0.001	0.14	NS	0.82	<0.001
TAG (mg/dL)	−0.23	NS	0.54	<0.001	−0.1	NS	0.56	<0.001
HDL (mg/dL)	−0.17	NS	−0.75	<0.001	−0.04	NS	−0.76	<0.001
LDL (mg/dL)	0.29	NS	0.46	<0.001	0.15	NS	0.47	<0.001
VLDL (mg/dL)	0.23	NS	0.54	<0.001	−0.10	NS	0.56	<0.001
TC/HDL-C	0.3	NS	0.5	<0.001	0.2	NS	0.6	<0.001
LDL-C/HDL-C	0.19	NS	0.5	<0.001	0.16	NS	0.5	<0.001
Cr (mg/dL)	−0.49	NS	0.31	NS	−0.04	NS	−0.15	NS
Urea (mg/dL)	−0.68	NS	0.19	NS	−0.035	NS	−0.25	NS

Note: CAD, Coronary artery disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; TC, total cholesterol; TAG, triacylglycerols; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low density lipoprotein; TC/HDL-C, risk factor-1; LDL-C/HDL-C, risk factor-2; Cr, creatinine; NS, not significant.

On performing multiple linear stepwise regression analysis using chemerin as the dependent variable, and age, BMI, FPG, HbA1c, TC, TAG, HDL-C, LDL-C, and VLDL-C as independent variables, only HbA1c remained significantly associated with chemerin (β = 0.482, P < 0.001).

Regarding apelin, there were significant positive correlations between serum apelin levels and BMI, FBG, HbA1c, TC, TAG, LDL-C, VLDL-C, TC/HDL-C, and LDL-C/HDL-C, along with a negative correlation with HDL-C in CAD II group. On the other hand, no significant correlation was observed between apelin levels and the clinical and biochemical characteristics of the study participants in CAD I group.

Multiple linear stepwise regression analyses using apelin as the dependent variable and age, BMI, FPG, HbA1c, TC, TAG, HDL-C, LDL-C, and VLDL-C as independent variables, indicated that apelin remained significantly associated with BMI (β = 0.65, P < 0.001), FPG (β = 0.24, P < 0.001), TC (β = 0.17, P < 0.001), and HDL-C (β = −0.16, P < 0.001).

Correlation analyses of vaspin and omentin-1 with the clinical and biochemical characteristics of the study participants

As shown in Table 4, Spearman's correlation test indicated the presence of significant negative correlations between serum vas-

Table 4. Correlation analyses of vaspin and omentin-1 with the clinical and biochemical characteristics of the study participants.

	Vaspin (ng/mL)				Omentin-1 (ng/mL)			
	CAD I		CAD II		CAD I		CAD II	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Age (years)	−0.006	NS	−0.025	NS	0.14	NS	−0.09	NS
BMI (kg/m^2)	−0.04	NS	−0.68	<0.001	−0.07	NS	−0.69	<0.001
SBP (mm Hg)	−0.028	NS	−0.026	NS	0.068	NS	−0.13	NS
DBP (mm Hg)	−0.027	NS	0.018	NS	0.07	NS	0.10	NS
FPG (mmol/L)	−0.08	NS	−0.65	<0.001	−0.05	NS	−0.66	<0.001
HbA_{1c} (%)	−0.17	NS	−0.5	<0.001	−0.13	NS	−0.72	<0.001
TC (mg/dL)	−0.18	NS	−0.7	<0.001	−0.15	NS	−0.72	<0.001
TAG (mg/dL)	0.09	NS	−0.53	<0.001	0.12	NS	−0.55	<0.001
HDL (mg/dL)	0.11	NS	0.46	<0.001	0.09	NS	0.62	<0.001
LDL (mg/dL)	0.19	NS	−0.6	<0.001	−0.17	NS	−0.6	<0.001
VLDL (mg/dL)	0.09	NS	−0.52	<0.001	−0.12	NS	−0.55	<0.001
TC/HDL-C	−0.17	NS	−0.6	<0.001	−0.3	NS	−0.6	<0.001
LDL-C/HDL-C	−0.008	NS	−0.5	<0.001	0.05	NS	−0.56	<0.001
Cr (mg/dL)	−0.36	NS	0.27	NS	0.08	NS	0.20	NS
Urea (mg/dL)	−0.23	NS	0.73	NS	0.04	NS	0.16	NS

Note: CAD, Coronary artery disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; TC, total cholesterol; TAG, triacylglycerols; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low density lipoprotein; TC/HDL-C, risk factor-1; LDL-C/HDL-C, risk factor-2; Cr, creatinine; NS, not significant.

pin levels and BMI, FBG, HbA1c, TC, TAG, LDL-C, VLDL-C, and atherosclerotic risk ratios together with a significant positive correlation with HDL-C in CAD II group. However, there was no significant correlation between serum vaspin levels and the clinical and biochemical characteristics of the study participants in CAD I group.

Furthermore, in multiple linear stepwise regression analysis using vaspin as the dependent variable and age, BMI, FPG, HbA1c, TC, TAG, HDL-C, LDL-C, and VLDL-C as independent variables, no significant correlation was obtained.

Similarly, there were significant negative correlations between serum omentin-1 levels and BMI, FBG, HbA1c, TC, TAG, LDL-C, VLDL-C, TC/HDL-C, and LDL-C/HDL-C and a significant positive correlation with HDL-C in CAD II group. No significant correlation was observed between omentin-1 level and the clinical and biochemical characteristics of the study participants in CAD I group. On performing multiple linear stepwise regression analysis using omentin-1 as the dependent variable and age, BMI, FPG, HbA1c, TC, TAG, HDL-C, LDL-C, and VLDL-C as independent variables, only BMI ($\beta = 0.16$, $P < 0.001$) and FPG ($\beta = 0.16$, $P < 0.001$) remained significantly associated with omentin-1.

Correlation analyses between the serum levels of chemerin, apelin, vaspin, and omentin-1 in CAD II patients

Data presented in Fig. 1 indicated that both chemerin and apelin were positively correlated to each other while they were negatively correlated to both vaspin and omentin-1. Additionally, omentin-1 was positively correlated to vaspin. On performing multiple linear stepwise analysis, using chemerin as the dependent variable, and apelin, vaspin, and omentin-1 as independent variables, only a strong negative association between chemerin and vaspin was obtained ($\beta = -0.36$, $P \leq 0.001$). On using apelin as the dependent variable, only omentin-1 remained associated with apelin ($\beta = -0.23$, $P \leq 0.001$). Meanwhile, when vaspin was the dependent variable, a strong positive association between vaspin and omentin-1 ($\beta = 0.7$, $P \leq 0.001$) was observed.

Receiver-operating characteristic curve analyses of serum chemerin, apelin, vaspin, and omentin-1 in CAD II patients

Based on analyses of the receiver operating characteristic curves, serum chemerin level with cut-off value ≥ 1.2 ng/mL predicted the presence of CAS in obese T2DM patients with AUC = 0.986, sensitivity = 95.7%, and specificity = 87% at $P \leq 0.001$. Meanwhile, the optimal cut-off value of serum apelin was ≥ 2.11 ng/mL, AUC = 0.94, sensitivity = 94%, and specificity = 90% at $P \leq 0.001$. Regarding serum vaspin level, the cut-off value was ≤ 2.2 ng/mL, AUC = 0.966, sensitivity = 79% and specificity = 96% at $P \leq 0.001$. Finally, serum omentin-1 showed cut-off value ≤ 1.3 ng/mL with AUC = 0.935, sensitivity = 95%, and specificity = 15.6% at $P \leq 0.001$.

Discussion

It is now clear that adipose tissue is a complex and highly active metabolic and endocrine organ that secretes a variety of adipokines, which have widespread effects on carbohydrates and lipid metabolism and appear to play an important role in the pathogenesis of insulin resistance, diabetes, inflammation, vascular endothelial dysfunction, and atherosclerosis (Raucci et al. 2013). Dysregulation of these pro-inflammatory and anti-inflammatory adipokines in obesity may serve as a link between obesity, insulin resistance, and CVD (Mattu and Randeva 2013).

In the present study, serum levels of chemerin were found to be significantly higher in both CAD I and CAD II groups compared with normal control group. Additionally, patients in CAD II group showed significantly higher serum levels of such adipokine compared with patients in CAD I group. Our results are in harmony with recent studies that showed elevated serum chemerin levels in type 2 diabetic Egyptian patients with and without ischemic heart disease (El-Mesallamy et al. 2011), and in type 2 diabetic Egyptian patients with subclinical atherosclerosis (Lachine et al. 2016). Such increase was attributed to the higher activity of the serine protease concerned with the activation of chemerin and, consequently, increased active chemerin levels (El-Mesallamy et al. 2011).

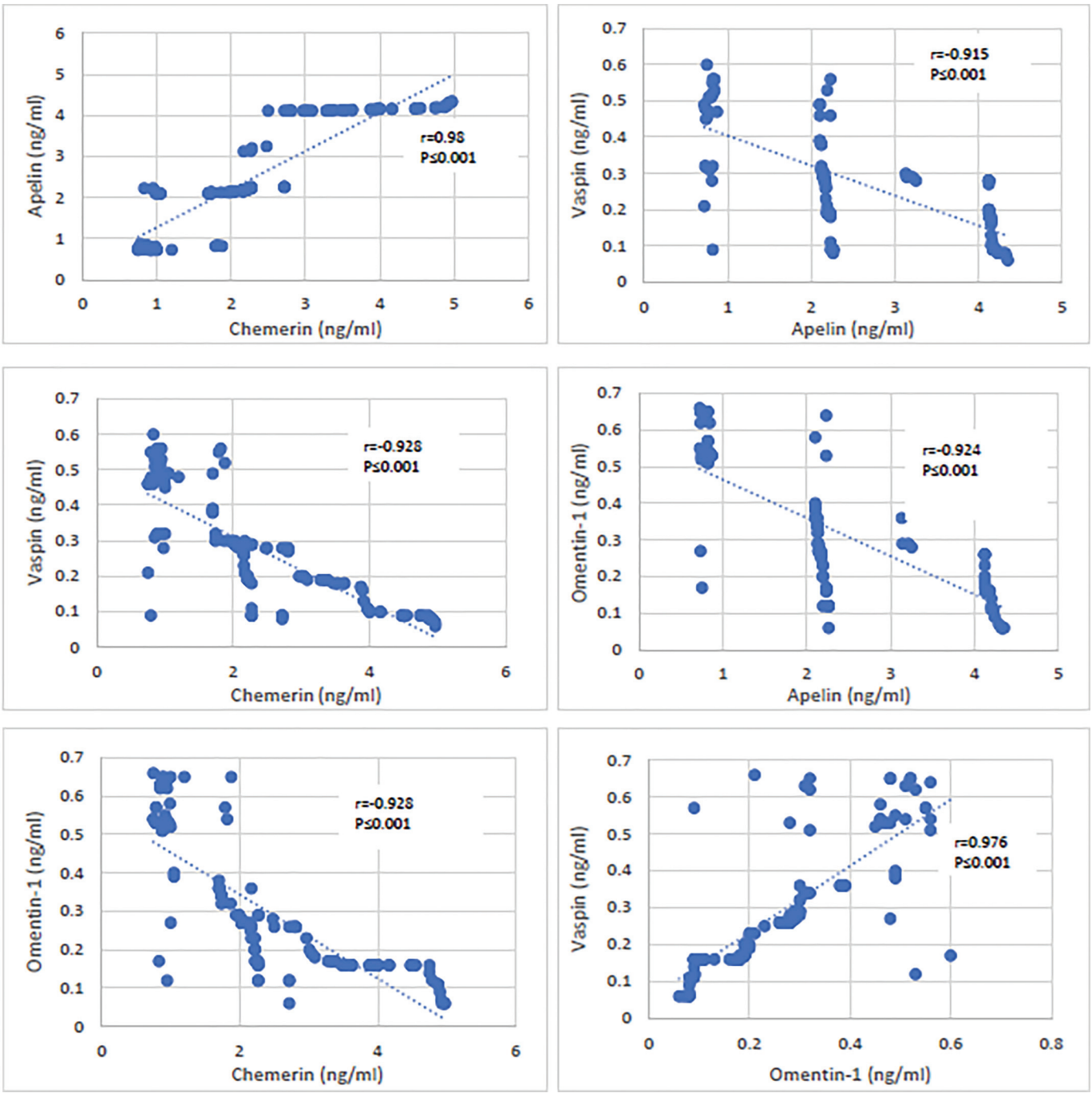
A possible role for local chemerin in atherosclerosis was suggested since high chemerin levels were observed in epicardial adipose tissues and vascular smooth muscle cells in the proximity of atherosclerotic lesions (Kostopoulos et al. 2014). The contribution of chemerin to the progression of atherosclerosis was thought to be mediated via stimulating the adhesion of macrophages to fibronectin and VCAM-1, increasing the expressions E-selectin and ICAM-1 (Landgraf et al. 2010), regulating angiogenesis, and activating MMP-2 and MMP-9 that play a critical role in plaque instability (Kaur et al. 2010).

In the current investigation, chemerin levels were found to be positively correlated with obesity and T2DM, which are 2 risk factors for stenosis. Interestingly, Boutsikou et al. (2013) suggested that elevated chemerin levels in "large for gestational age infants" possibly imply the predisposition to insulin resistance and thus may serve as an early prognostic marker for development of metabolic syndrome in the future.

Our findings also demonstrated that chemerin levels were positively associated with TC, TAG, LDL-C, and VLDL-C as well as the atherosclerotic risk factors and negatively correlated with HDL-C, indicating a direct association between chemerin levels and development of stenosis in obese Egyptian patients with T2DM. These results come in agreement with those of similar studies on obese type 2 diabetic Egyptian patients with ischemic heart disease (El-Mesallamy et al. 2011) and obese diabetic Korean patients with CAD (Hah et al. 2011).

In the present study, significantly higher serum levels of apelin were observed in both CAD I and CAD II patients compared with the normal controls. In addition, CAD II patients exhibited significantly higher levels of this adipokine compared with CAD I patients. Our results confirmed those reported by Abd-Elbaky et al.

Fig. 1. Correlation analyses between the serum levels of chemerin, apelin, vaspin, and omentin-1 in coronary artery disease (CAD) II patients. [Colour online.]



(2015) in obese type 2 diabetic Egyptian patients with CVD. Likewise, circulating apelin was found to be higher in obese type 2 diabetic French patients (Habchi et al. 2014). On the contrary, El-Mesallamy et al. (2013) found decreased serum apelin levels in type 2 diabetic Egyptian postmenopausal women with CAD. Such discrepancies could be attributed to gender variations, the use of ELISA kits with different characteristics, different atherosclerotic index evaluation methods, or the small sample size used in each study.

Our results also revealed that apelin was positively correlated with obesity, T2DM, TC, TAG, LDL-C, VLDL-C, and atherosclerotic risk ratios and negatively correlated with HDL-C in CAD II patients, which are important factors for the development of atherosclerotic plaque. These findings are in harmony with those of Abd-Elbaky et al. (2015). On the same line, apelin has been implicated in the development of atherosclerosis since it was found to promote the progression of atherosclerosis in vitro (Li et al. 2012) and correlate with oxidative stress and inflammation markers (García-Díaz et al. 2007). Additionally, Dray et al. (2010) have suggested that increased apelin levels could constitute a compensatory mechanism to reduce insulin resistance in T2DM. However, the study by Briana and Malamitsi-Puchner (2009) suggested that apelin may not be directly involved in the regulation of insulin sensitivity in the perinatal period.

The current investigation may be the first to demonstrate that Egyptian patients with CAS both non-obese nondiabetic and obese

with T2DM exhibited significantly lower serum vaspin levels compared with healthy controls. Our results are in harmony with the recent findings in which low serum vaspin levels were found in type 2 diabetic Indian patients with acute coronary syndrome, suggesting that vaspin has anti-atherosclerotic and anti-inflammatory properties (Sathyaseelan et al. 2016). Indeed, lower levels of vaspin have been reported in other inflammatory states including spontaneous delivery term inflammation (Briana et al. 2011). Actually, multiple lines of evidence suggested that vaspin protects endothelial cells from inflammation and apoptosis (Heiker 2014). The anti-atherogenic effect of vaspin has been attributed to activation of AMPK, followed by NF-kB inhibition and attenuation of cytokine-induced adhesion molecule gene expressions (Jung et al. 2014).

Our data also showed that vaspin was negatively correlated with T2DM, obesity, TC, TAG, LDL-C, VLDL-C, and atherosclerotic risk ratios, while was positively correlated to HDL-C in CAD II patients. In agreement with these findings, vaspin was reported to be negatively correlated with FPG and BMI in obese newly diagnosed type 2 diabetic patients (Tasnim et al. 2015), and positively correlated to HDL-C in obese individuals with abnormal glucose tolerance (Sperling et al. 2016).

Our fourth adipokine of interest in the current study is omentin-1. Significantly lower serum levels of omentin-1 were found in both CAD I and CAD II patients compared with healthy controls with more significant reduction in CAD II patients than CAD I patients. Comparable results were reported in previous studies on Egyptian type 2 diabetic patients with ischemic heart disease (El-Mesallamy et al. 2011) and CVD (Abd-Elbaky et al. 2015). In addition, in Saudi Arabia's population there was a tendency for a fall in serum omentin-1 concentration with increasing coronary risk in obese type 2 diabetic patients with CVD (Alissa et al. 2016). Actually, omentin-1 has been shown to inhibit TNF-α-induced vascular inflammation in human endothelial cells in vitro (Yamawaki et al, 2011), suggesting that decreased level of omentin-1 may contribute to the pathogenesis of atherosclerosis. Additionally, omentin-1 has been proposed to be a biomarker for CAD (Shibata et al. 2011). On the contrary, a recent study concluded that coronary patients with high plasma omentin had significantly more cardiovascular events than patients with low plasma omentin (Saely et al. 2016). Nonetheless, the relation between omentin-1 and CAD needs to be further investigated.

In the current study, significant negative correlations were observed between serum omentin-1 levels and BMI, FBG, HbA1c, TC, TAG, LDL-C, VLDL-C, TC/HDL-C, and LDL-C/HDL-C together with a positive correlation with HDL-C in CAD II patients. In accord with our results, omentin-1 has been reported to be negatively correlated with BMI, FPG, and TAG and positively correlated with HDL-C in obese subjects with subclinical inflammation (Alissa et al. 2016).

Another interesting finding in the present study is the existence of a sort of interplay between the 4 adipokines. Thus, strong negative correlations were observed between chemerin and vaspin and between apelin and omentin-1, together with a strong positive correlation between vaspin and omentin-1. Such findings indicate, maybe for the first time, a potential cross talk occurring between these 4 adipokines in the pathogenesis of CAS in obese type 2 diabetic Egyptian patients. Recently, omentin-1 was reported to be negatively associated with apelin in obese type 2 diabetic Egyptian patients with CVD (Abd-Elbaky et al. 2015). Yet, further experimental and clinical studies with larger sample size are needed to identify the precise molecular mechanism underlying the interplay between these adipokines.

Finally, the current study demonstrated the ability of serum chemerin, apelin, vaspin, and omentin-1 levels to differentiate obese type 2 diabetic patients with CAS from both controls and non-obese nondiabetic patients with CAS. Among the 4 adipokines, chemerin exhibited the highest potential, followed by vaspin, suggesting the usefulness of both adipokines as additional biomarkers for diagnosis of CAS in obese patients with T2DM.

Conclusion

Higher serum levels of chemerin and apelin along with lower serum levels of vaspin and omentin-1 were found to be associated with CAS in obese Egyptian patients with T2DM, suggesting that alterations in the levels of these 4 adipokines might have predisposed those patients to the pathogenesis of CAS. Strong negative correlations were observed between chemerin and vaspin and between apelin and omentin-1, together with a strong positive correlation between vaspin and omentin-1 signifying crosstalk between these 4 adipokines in obese, type 2 diabetic patients with CAS. However, the precise molecular mechanism underlying the role of such interplay in CAS needs to be further elucidated. Finally, the study highlights the potential usefulness of both chemerin and vaspin as additional noninvasive biomarkers to support diagnosis of CAS in obese Egyptian patients with T2DM.

Conflict of interest

The authors declare that there is no conflict of interest associated with this work.

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