LUPINE PUBLISHERS
Open Access

Archives of Organic and Inorganic Chemical Sciences

DOI: 10.32474/AOICS.2018.01.000111

ISSN: 2637-4609

Mini Review

Level of Some Adipokines in Obese Type 2 Diabetic Egyptian Patients with Coronary Artery Stenosis

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Received: January 16, 2018; **Published:** February 05, 2018

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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. Cardiovascular diseases 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. Type 2 diabetes mellitus (T2DM) is usually proceeded with a state of insulin resistance or insufficient insulin signal pathways that plays a crucial role in the pathogenesis of the disease and its associated complication. Obesity is a chronic serious and growing problem of excessive body fat which has been linked with dyslipidaemia, CVD and diabetes. Besides, white adipose tissue (WAT) is recognized as an important player in obesity-mediated and CVD. It is well established that WAT is an active endocrine organ that contributes to the inflammatory process in obese subjects and secretes a variety of adipokines. These adipokines including chemerin, vaspin, omentin-1 and apelin affect the whole-body homeostasis by influencing numerous physiological and biological processes and fulfilling their actions via different signaling pathways and chemical mediators. According to the latest WHO data published in 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 four aforementioned adipokines may differ between obese type 2 diabetic Egyptian patients with coronary artery stenosis (CAS) and healthy controls since such patients have increased fat mass, altered insulin resistance and inflammatory milieu. Therefore, the present study was designed to assess the circulating levels of chemerin, apelin, vaspin and omentin-1 in obese type 2 diabetic Egyptian patients with coronary artery stenosis (CAS). The study also aimed at investigating the possible correlation between these four adipokines and the clinical and biochemical characteristics of those patients in a hope to provide a better understanding for the potential usefulness of these adipokines as non-invasive diagnostic biomarkers for CAS in obese T2DM Egyptian patients. The present study included 120 Egyptian participants (48 men and 72 women) aged 45-65. 90 patients with CAS and 30 healthy control subjects. 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.

Patients with CAS were further classified into two groups:

i. Group I (CAD I): included 45 non-obese, non-diabetic patients with CAS.

ii. Group II (CAD II): included 45 obese, type 2 diabetic patients with CAS. 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.

The following parameters were performed for all subjects:

i. Full clinical examination.

ii. FPG and HbA1c levels.

iii. Lipid profile that includes: Total cholesterol (TC), triacylglycerol (TAG), high density lipoprotein cholesterol (HDL-C). Low density lipoprotein-cholesterol (LDL-C) and very low-density lipoprotein-cholesterol (VLDL-C) were calculated using the Friedewald equation.

iv. Kidney function tests that includes: serum creatinine (Cr) and urea.

v. Serum chemerin, apelin, vaspin, and omentin-1 levels were estimated using ELISA technique.

Results of the present study revealed that CAD I patients showed higher TC, TAG, LDL-C, VLDL-C and atherosclerotic risk ratios TC/HDL-C and LDL-C/HDL-C compared to normal subjects. Furthermore, compared to both controls and CAD I patients, CAD II patients showed significantly higher FBG, HbA1c, TC, TAG, LDL-C, VLDL-C as well as atherosclerotic risk ratios. On the other hand, HDL-C was significantly lower in CAD II group compared to either normal or CAD I groups. In the current study, serum levels of chemerin and apelin were significantly higher in both CAD I and CAD II groups compared to normal control group. Additionally, CAD II patients showed significantly higher levels of both adipokines compared to CAD I patients. On the other hand, serum levels of vaspin and omentin-1 were significantly lower in CAD I and CAD II patients compared to normal controls. Additionally, patients in CAD II group exhibited significantly lower values for vaspin and omentin-1.

Spearmen'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. Meanwhile, no significant correlation was observed between serum chemerin levels and the clinical and biochemical characteristics of the study participants in CAD I group. 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. Additionally, Spearmen correlation test indicated the presence of significant negative correlations between serum vaspin 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.

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. Our results also, 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. In the current study, based on analyses of the ROC curves, serum chemerin level with Cut off value ≥ 1.2 ng/ml predicted the presence of CAS in obese type 2 diabetic patients with AUC=0.986, sensitivity=95.7%, and specificity=87% at P≤0.001. Meanwhile, the optimal Cut off value of serum apelin was ≥ 2.11ng/ml, AUC=0.94, sensitivity=94% and specificity=90% at P≤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≤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≤0.001.

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 lipids metabolism and appear to play an important role in the pathogenesis of insulin resistance, diabetes, inflammation, vascular endothelial dysfunction and atherosclerosis. Dysregulation of these pro-inflammatory and anti-inflammatory adipokines in obesity, may serve as a link between obesity, insulin resistance and CVD. In the present study, serum levels of chemerin were found to be significantly higher in both CAD I and CAD II groups as compared to normal control group. Additionally, patients in CAD II group showed significantly higher serum levels of such adipokine compared to patients in CAD I group. Our results are in harmony with recent studies that showed elevated serum chemerin levels in Egyptian T2DM patients with and without ischaemic heart disease and in T2DMEgyptian patients with subclinical atherosclerosis. Such increase was attributed to the higher activity of the serine proteases concerning activation of chemerin and consequently increased active chemerin levels. Likewise, a study on Korean patients reported that serum chemerin levels were significantly higher in obese diabetic patients with coronary artery disease .A possible role for local chemerin in atherosclerosis has been suggested since high chemerin levels were observed in epicardial adipose tissues, foam cells and vascular smooth-muscle cells in the proximity of atherosclerotic lesions. 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, activating MMP-2 and MMP-9 that play a critical role in plaque instability and regulating angiogenesis.

However, a recent study by indicated that the use of chemerin as an independent predictor of cardiovascular event risk should be further investigated. In the current investigation, chemerin levels were found to be positively correlated with obesity and T2DM which are two risk factors for stenosis. Moreover, 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 link between chemerin levels and development of stenosis in obese T2DM patients. These results come in agreement with those of *El-Mesallamy et al*. who suggested that elevated chemerin in obese T2DM patients with ischaemic heart disease might be a link between obesity and inflammation. Similarly, positive correlations were reported by *Hah et al.*

between serum chemerin levels and FPG, TC, LDL-C and TAG but did not correlate significantly with HDL-C and BMI. Results of the present study showed significantly higher serum levels of apelin in both CAD I and CAD II groups compared to the normal controls. Moreover, CAD II patients exhibited significantly higher levels of this adipokine compared to CAD I patients. Our results confirmed those reported by *Abd-Elbaky et al*. who demonstrated higher serumapelin levels in obese T2DM Egyptian patients with CVD. On the same line altered glucose homeostasis has been shown to be associated with increased apelin serum levels in T2DM Italian patients. Likewise, apelin levels were found to be higher in obese T2DM French population. On the contrary, *El Mesallamy et al*. found decreased serum apelin levels in non-obese and obese T2DM Egyptian patients with CAD. Such discrepancies could be attributed to the use of ELISA kits with different characteristics, different atherosclerotic index evaluation methods used 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, atherosclerotic risk ratios and negatively correlated with HDL-C in CAD II patients which are important factors for the development of atherosclerotic plaque. Previous study by Dray et al. indicated that in humans, plasma apelin correlated positively with HbA1c% and suggested that increased apelin levels could constitute a compensatory mechanism to reduce insulin resistance in T2DM.

Meanwhile, apelin was found to be positively associated with BMI, TAG in obese T2DM Egyptian patients. Additionally, *In vitro* study demonstrated that apelin promoted cholesterol efflux and induced foam cells formation as well as the progression of atherosclerosis. Moreover, study by *García-Díaz et al*. implicated apelin in the development of atherosclerosis, since apelin was correlated with oxidative stress and inflammation markers in this study. The current investigation may be the first to demonstrate that Egyptian patients with CAS either non-obese non-diabetic or obese T2DM exhibited significant lower serum vaspin levels compared to healthy controls. Our results are in harmony with the recent findings in which low serum vaspin levels were found in T2DM Indian patients with acute coronary syndrome suggesting that vaspin has anti-atherosclerotic and anti-inflammatory properties. Actually, multiple lines of evidence suggested that vaspin protects endothelial cells from inflammation and apoptosis. The anti-atherogenic effect of vaspin has been attributed to activation of adenosine monophosphate-activated protein kinase (AMPK) followed by NF-kB inhibition and attenuation of cytokine induced adhesion molecules gene expressions. 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. On the same line, vaspin was negatively correlated to FPG and BMI in obese diabetic Bangladeshi population, these authors had implicated the low vaspin levels in the development of insulin resistance, obesity and the progression of T2DM. In addition, vaspin was positively correlated to HDL-C in obese subjects with up normal glucose tolerance in Polish population. Our fourth adipokine of interest in the current study was omentin-1. Significant lower serum levels of this adipokine was demonstrated in both CAD I and CAD II patients compared to controls with more significant reduction in CAD II patients compared to CAD I.

Comparable results were reported in two studies on Egyptian T2DM patients with ischaemic heart disease and with CVD. Moreover, in Saudii population there was a tendency for a fall in serum omentin-1 concentration with increasing coronary risk in obese T2DM with CVD patients. *In vitro* study, has shown that omentin-1 inhibited TNF-α induced vascular inflammation in human endothelial cells and thus decreased level of omentin-1 may contribute to the pathogenesis of atherosclerosis. Additionally, low omentin-1 levels have been suggested to be a biomarker for CAD. Moreover, on the contrary a recent prospective study concluded for the first time that elevated plasma omentin-1 predicts independently the presence and extent of angiographic ally determined baseline CAD. However, future research should be done concerning this adipokine. In the current study, there was a significant negative correlation between serum omentin-1 levels and BMI, FBG, HbA1c, TC, TAG, LDL-C, VLDL-C, TC/HDL-C, LDL-C/HDL-C while a positive correlation with HDL-C in CAD II patients. In agreement with our results, omentin-1 has been found to be negatively correlated to BMI, FPG, TAG and positively correlated to HDL-C. Additionally, *Moreno-Navarrete et al.* found a negative correlation between omentin-1 levels and TC supporting that omentin-1 may play a regulatory role in lipid metabolism. Another interesting finding in the present study is a sort of interplay between the four adipokines thus strong negative correlations were observed between chemerin and vaspin and between apelin and omentin-1. Additionally, a strong positive correlation between vaspin and omentin-1. Such findings indicate may be for the first time a potential cross talk occurring between these four adipokines in the pathogenesis of CAS in obese T2DM Egyptian patients. Recently, it has been demonstrated that omentin-1 was negatively associated with apelin in obese T2DM Egyptian patients with CVD. However, further experimental and clinical studies with larger sample size should be performed to identify the precise molecular mechanism underlying the interplay between this adipokines. Finally, the current study demonstrated the ability of serum chemerin, apelin, vaspin and omentin-1 levels to differentiate obese T2DM patients with CAS from both controls and non-obese non-diabetic patients with CAS. Among the four adipokines chemerin exhibited the highest potential followed by vaspin suggesting the usefulness of both adipokines as additional biomarkers for diagnosis of CAS in obese T2DM patients.

Conclusion

The main findings of this study are:

a. 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 four adipokines might have predispose those patients to the pathogenesis of CAS.

b. 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 four 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.

c. Finally, the study highlights the potential usefulness of both chemerin and vaspin as additional non-invasive biomarkers to support diagnosis of CAS in obese Egyptian patients with T2DM.

DOI: 10.32474/AOICS.2018.01.000111