

Omentin and Apelin Concentrations in Relation to Obesity Diabetes Mellitus Type two and Cardiovascular Diseases in Egyptiant Population

Abstract

Background and aim: The goal of this study was to evaluate the role of serum Omentin and apelin in obese patients having type 2 diabetes mellitus with and without cardiovascular disease compared to the healthy control group and evaluation of their association with selected anthropometric, biochemical, and clinical parameters.

Methods: A total of 240 adults sex and age-matched were included in the current case-control study. 80 of which served as healthy non-obese controls. Patients enrolled in the study were classified into the following groups: 80 type 2 diabetic obese subjects without cardiovascular disease and 80 type 2 diabetic obese subjects with cardiovascular disease. Fasting blood sample was collected to determine biochemical indicators and insulin resistance index (HOMA-IR). Omentin, apelin, interleukin-1 β (IL-1 β), troponin-T, and oxidized LDL (Ox-LDL) plasma level was assessed by ELISA. Association of adipokines with biochemical markers was studied.

Results: Levels of Omentin were lower in obese diabetic groups than non-obese controls. On the other hand apelin and IL-1 β levels showed higher significant values in obese diabetic groups compared to healthy ones. In correlation analysis, Omentin was negatively associated with insulin resistance index, apelin, and troponin-T. On the other hand, apelin was positively associated with IL-1 β , BMI, and troponin-T.

Conclusion: Our study supports the hypothesis that deregulated production of adipokines; Omentin and apelin owing to adipose tissue dysfunction can contribute to the pathogenesis of obesity-linked complications that may lead eventually to type 2 diabetes mellitus and cardiovascular disease.

Keywords: Cardiovascular disease; Omentin; Apelin; IL-1 β ; Troponin-T; Ox-LDL; Obesity; Type 2 diabetes mellitus

Review Article

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**Atif E Abd-Elbaky¹, Dina M Abo-ElMatty²,
Noha Mostafa Mesbah² and Sherine M
Ibrahim^{3*}**

¹Department of Biochemistry, Suez Canal University, Egypt

²Department of Biochemistry, Portsaid University, Egypt

³Faculty of Pharmacy, Modern Sciences and Arts University, Egypt

***Corresponding author:** Sherine M Ibrahim, Faculty of Pharmacy, Modern Sciences and Arts University, Cairo, Egypt, Email: catsshery@yahoo.com

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Abbreviations: T2DM: Type 2 Diabetes Mellitus; IR: Insulin Resistance; DM: Diabetes Mellitus; CVD: Cardiovascular Disease; TAG: Triacyl Glycerol; HOMA: Homeostasis Model Assessment; BMI: Body Mass Index; HDL: High-Density-Lipoprotein; TC: Total Cholesterol; Ox-LDL: Oxidized LDL

Introduction

Obesity is a chronic disease of multi factorial origin [1]. It's now widely accepted that obesity is associated with many metabolic disorders including type 2 diabetes mellitus (T2DM) [2]. The major link between obesity and T2DM is insulin resistance (IR). Adipose tissue depots are the most vulnerable target to mediate significant immune cells infiltration and inflammation contributing to systemic inflammation and IR in obese humans [3]. Diabetes has become an epidemic and remains a major public health issue. In 2010, it was estimated that 4.787 million Egyptians (10.4 % of the Egyptian population) had diabetes and that diabetes will increase to 8.615 million Egyptians by the year 2030 [4]. Diabetes mellitus increases the incidence of coronary heart disease, being the most common

and clinically important complication in DM [5].

Adipose tissue represents an active endocrine organ by releasing the large number of bioactive mediators (adipokines) that plays an important role in modulating glucose metabolism and inflammation [6]. The adipokines secretion pattern reflects adipose tissue function and seems to be important for determining the individual risk to develop metabolic and cardiovascular co morbidities of obesity [7]. When adipose tissue inflammation and dysfunction have developed, adipokines secretion is significantly changed towards a diabetogenic, pro-inflammatory, and atherogenic pattern [8]. Among the adipokines of recent discovery, Omentin, apelin, and IL-1 β seem to have a key role in the cardiovascular disease (CVD) pathophysiology [9]. Omentin is a newly identified secretory protein that is relative to subcutaneous adipose tissue and is highly and selectively expressed in visceral adipose tissue.

Low Omentin expression was observed in obesity, IR and T2DM [10]. It was shown that Omentin levels correlate inversely with troponin-T and total cholesterol in obese patients with

heart disease. There was an observation that Omentin has anti-inflammatory, anti-atherogenic, and anti-diabetic properties [11]. The other newly discovered adipokines, apelin-12 is a novel 12-amino peptide expressed in adipocytes of humans; it is encoded by the APLN gene [12]. The synthesis of apelin in adipocytes is triggered by insulin and its plasma levels are reported to increase in association with insulin resistance, hyperinsulinemia, and diabetes mellitus [13]. Our previous studies indicated that in T2DM patients, with or without CVD, the concentration of apelin was significantly increased [14]. And positively correlated with concentration of pro-inflammatory cytokine, IL-1 β as well as negatively correlated with triacylglycerol (TAG) and BMI [15]. Apelin was up-regulated in the atherosclerotic coronary artery and this peptide localized to the plaque with markers for macrophages and smooth muscle cells [16]. Epidemiological studies showed that IL-1 β as a pro-inflammatory cytokine was significantly increased and correlated with Troponin-T and Ox-LDL in obese diabetic patients [17]. IL-1 β has been reported to contribute to β -cell failure and has also been implicated in the progression of atherosclerosis and heart failure [18]. The present work aimed to study the association between novel adipokines and obesity and its diabetic and cardiovascular complications in Egyptian population.

Subjects and Methods

Study design

A total of 240 Egyptian adults' men were included in this case-control study. Subjects were selected according to our defined inclusion criteria which was: age 35-45 years. 80 of which served as healthy non-obese controls. Patients enrolled in the study were classified into the following groups: 80 type 2 diabetic obese subjects without CVD (T2DM group), they were selected from patients attending the Endocrinology Department of Suez Canal University hospitals and 80 type 2 diabetic obese subjects with CVD (T2DM + CVD group) admitted to the Intensive Care Unit-Cardiology Department. A patient was considered to have CVD if he had history of myo-cardial infarction or the diagnosis was based on the result of coronary angiography.

Exclusion criteria were defined as: having the history of any condition that affects inflammatory markers such as known cardiovascular diseases, thyroid diseases, malignancies, current smoking, heart failure, acute or chronic infections, acute or chronic inflammatory disease, hepatic or renal diseases, and alcohol or drug abuse. We limited our study to non smokers. The study was approved by the Committee on Medical Ethics of Suez Canal University. The study was carried out in accordance with the regulations and recommendations of the Declaration of Helsinki. All subjects gave their written informed consent prior to participation. A detailed medical history and drug treatment (s) were collected for all subjects. Body mass index (BMI) of all Subjects was calculated as weight (kg)/height (m²) and subjects with BMI equal or more than 30 kg/m² were considered as obese subjects and placed in obese diabetic group. The control group was those with BMI lower than 30 kg/m².

Biochemical assay

The peripheral blood samples were obtained following 10-12

hours overnight fasting. Serum was separated, aliquot and stored at -80°C. All samples were analyzed by means of a single assay. Standard enzymatic techniques were used for the measurement of fasting serum glucose (FBG) [19] and lipids [total cholesterol (TC) [20] and TAG [21]. High-density-lipoprotein (HDL) was determined after precipitation of Apo lipoprotein B-containing lipoproteins [22]. The reference values for the lipid profile were according to established guidelines [23]. Serum insulin concentrations were measured by ELISA method (Human insulin ELISA kit, Moonblind, Inc., USA) with a minimum detectable concentration of 1.76 mIU/ml.

Homa calculation

Insulin resistance was calculated by homeostasis model assessment (HOMA). The HOMA IR was calculated according to HOMA IR equation= [Fasting Plasma Glucose (mg/dL) \times Fasting Plasma Insulin (mIU/mL)] /405 [24].

Cardiovascular Markers Determination

Troponin-T as well as Ox-LDL was measured in serum aliquots kept frozen at -80°C using ELISA kit (Myo Bio Source, Inc, USA) according to manufacturer's instructions (R&D Systems, Wiesbaden, Germany).

Adipokine Determination

Inflammatory Cytokine; IL-1 β [25] was measured by ELISA kit (Boaster Biological Technology, Inc, USA). As for novel adipokines; serum Omentin levels [26] were measured by ELISA kit (Alpco Diagnostics, Inc, USA) with sensitivity of 0.4 ng/ml. while serum apelin-12 levels [27] were measured by ELISA kit (MyoBioSource, Inc, USA). The sensitivity of the assay was 0.2 ng/ml and the inter-assay error was below 5%.

Statistical analysis

Data are presented as mean \pm SD, range. Measured parameters levels between groups were compared with student's t-test. Correlation analyses between Omentin and apelin levels and other laboratory values or patient characteristics employed Pearson's correlation coefficient values less than 0.05 were considered to be statistically significant. A multiple linear regression analysis was performed to investigate independent association between serum apelin and Omentin levels (dependent variable) and selected variables that had p-values <0.05 in univariate analysis (sex and age were also included). P-values <0.05 were considered statistically significant with a confidence interval of 95%

Results

A total of 240 subjects were included in this study, the clinical and demographic data of the study population. Patients and controls differed significantly in all conventional risk factors for obesity complications including BMI, hypertension, FBG, insulin, HDL, TAG, and TC (P < 0.05). Hypertension was defined as a systolic blood pressure (BP) \geq 140 mmHg, a diastolic BP \geq 90 mmHg, or both. In diabetic groups a significantly higher levels of FBG and insulin was observed. Measuring the insulin resistance state by HOMA IR showed higher significant levels in diabetic groups compared to control ones (P < 0.05). In addition here

were no significant differences in the baseline characteristics between diabetic patients and controls in terms of age, sex and duration of diabetes. Regarding cardiovascular makers there was a significant increase in troponin-T levels in T2DM group (0.69 ± 0.05 ng/mL) and T2DM + CVD group (4.71 ± 1.02 ng/mL) compared with control group (0.008 ± 0.01 ng/mL). Ox-LDL level in the diabetic groups increased by 2.9 fold the control level, respectively, ($P > 0.05$). Also T2DM + CVD group showed higher significant values of troponin-T and Ox-LDL compared to T2DM group. Regarding adipokines levels the inflammatory cytokine; IL-1 β level in groups T2DM and T2DM + CVD increased to 28.8 ± 2.34 and 29.7 ± 2.1 pg/mL, respectively compared to control group 19.17 ± 1.76 pg/mL. For Omentin, there was a significant decrease in group T2DM (23 ± 4.9 pg/mL) and T2DM + CVD levels (20.49 ± 5.4 pg/mL) compared with the control group level (58.8 ± 8 pg/mL). Regarding T2DM + CVD group apelin level, its elevation represented 2.5 and 1.2 folds control and T2DM group levels, respectively.

In the obese diabetic groups (T2DM, T2DM + CVD) (n=160) according to Pearson's correlation coefficient, Omentin levels were correlated significantly negatively with insulin ($r = -0.18$, $p = 0.01$), HOMA IR ($r = -0.19$, $p = 0.05$), troponin - T ($r = -0.26$, $p = 0.0001$) and TC levels ($r = -0.15$, $p = 0.05$). However, apelin level was correlated negatively significantly with Omentin ($r = -0.2$, $p = 0.05$) and positively with IL-1 β ($r = 0.15$, $p = 0.05$), troponin - T ($r = 0.28$, $p = 0.0001$), BMI ($r = 0.2$, $p = 0.01$), and TAG ($r = 0.2$, $p = 0.01$). Finally IL-1 β was correlated positively with troponin - T ($r = 0.16$, $p = 0.05$), Ox-LDL ($r = 0.15$, $p = 0.05$), and BMI ($r = 0.3$, $p = 0.0001$). There was no significant correlation between apelin and insulin as well as HOMA IR. Also there was no significant correlation between Omentin and IL-1 β . Multiple regression analysis with all the significant variables confirmed that BMI, TAG, troponin - T, and IL-1 β were all determinants of serum apelin levels independently from age, FBG, insulin, and TC. While serum Omentin levels were dependent on insulin, TC, and troponin - T as well as independent from age, BMI, FBG, and IL-1 β .

Discussion

Obesity is a chronic pathological condition and a risk factor for metabolic syndrome development, T2DM and CVD [28]. Several studies have shown that visceral obesity is strongly associated with IR, hyperglycemia, dyslipidemia, and hypertension [29]. Moreover, DM is one of the most common chronic diseases in nearly all countries; it is estimated that Egypt will be listed in the top 10 countries with the highest numbers of people with diabetes in 2030, reflecting anticipated changes in the population size and structure in Egypt [4]. Type 2 diabetes mellitus and its associated complications have become a public health problem of considerable magnitude. CVD causes most of the excess morbidity and mortality in DM [30]. The cardiovascular risk factors hypertension, dyslipidemia, obesity, IR, and hyperinsulinemia cluster in the Metabolic Syndrome [31]. All of these mentioned factors, being observed well in the current study, create a state of constant and progressive damage to the vascular wall ((increased troponin-T and Ox-LDL), manifested by a low-grade inflammatory process (increased IL-1 β).

Oxidative stress and the oxidation of low-density lipoprotein (LDL) play a role in atherosclerosis and associated risk factors [32]. It is worthy to state that Ox-LDL was significantly increased in the diabetic groups as compared to the control ones in our study. Our results revealed that troponin -T and Ox-LDL were significantly higher in T2DM + CVD group as compared to T2DM and control groups. This was also in support of the study conducted by [33] who stated that there is a strong clear association between cardiovascular abnormalities and troponin -T level. We sought to test the usefulness of IL-1 β in our population of diabetic patients. A recent study conducted by [15] have described a positive association between IL-1 β and obesity, suggesting functional effects on fat mass, fat metabolism and body mass. This is supported by the positive correlation found between IL-1 β and BMI in our study. However, it is known that adipose tissue can synthesize and release the main pro-inflammatory cytokines; IL-1 β which also impairs insulin secretion and induces β -cell apoptosis leading to T2DM [34].

Accumulating evidence indicates that the diseases related to metabolic syndrome are characterized by abnormal cytokine production, including elevated circulating IL-1 β ; this was also supported by who has shown that IL-1 β plays a role in diseases associated with metabolic syndrome such as atherosclerosis and T2DM. In our present study IL-1 β was positively correlated with troponin -T and Ox-LDL in our diabetic groups. According to [35] in addition to the effective pro-inflammatory adipokines described above, adipose tissues also secrete a smaller number of anti-inflammatory factors, such as Omentin, Omentin is a novel visceral fat depot-specific adipokines which is considered to be linked to T2DM in various populations. Omentin has been reported to have an association with visceral obesity, IR, and glucose metabolism [36]. In the present study, we demonstrated that circulating levels of Omentin was inversely correlated with a number of metabolic risk factors (TC and troponin -T). Individuals in our study with excess of visceral fat accumulation (diabetic groups) have a high risk of the development of metabolic syndrome in comparison with non-obese control group.

Our results showed that Omentin level was significantly reduced in the diabetic patients with and without CVD as compared to the healthy controls. Moreover, the negative correlation of troponin -T with Omentin in our diabetic groups is consistent with the study of [37] on the Chinese patients that showed that low levels of circulating Omentin are also associated with the prevalence of coronary artery disease. These data suggest that Omentin may represent a biomarker for not only metabolic disorders, but also CVD. In a study done by [38] on the obese Caucasian population, Omentin levels were found to be correlated with some markers of lipid metabolism such as TC which indicates that Omentin may play a role in lipid metabolism or diabetic dyslipidemia as a compensatory mechanism, this is consistent with our results which showed negative significant correlation between Omentin levels and TC levels in our obese diabetic groups.

A previous study conducted by [39] showed that decreased serum Omentin levels observed in obese humans might cause a reduction of insulin-stimulated glucose uptake in visceral

and subcutaneous adipocytes or other insulin sensitive tissues and contributing, at least partially, to insulin resistance and this was supported in our study by the negative correlation between Omentin levels and insulin levels as well as HOMA IR as an indicator of insulin resistance in our obese diabetic groups (T2DM and T2DM + CVD). According to [35] obesity leads to the down-regulation of anti-inflammatory factors, such as Omentin and the up-regulation of IL-1 β and apelin that activate endothelial cells and promote a dysfunctional phenotype. Apelin is another short peptide released from adipocytes originating from a 77-amino-acid precursor and its synthesis is stimulated by insulin. Collected data from both the clinical and basic research settings showed that apelin correlates with states of IR and obesity and decreases insulin secretion [40]. Recently, [41] disclosed a markedly increased plasma apelin level in obese T2DM subjects; this result was supported by the significant positive correlation between apelin and BMI as an indicator for obesity in our obese diabetic groups (T2DM and T2DM + CVD). The connection between apelin and T2DM has been postulated.

Meanwhile, we also found that apelin was significantly correlated with IL-1 β in our obese diabetic groups. Therefore, we speculated that apelin might be involved in the pathophysiologic process in obese T2DM patients, taking into account the role of IL-1 β in the development of IR and atherosclerosis. Although apelin has been viewed as a beneficial adipokines up-regulated in obesity as confirmed by [42]. Our results revealed that apelin has positive and negative significant correlation between troponin-T and Omentin in our diabetic groups, respectively. As new adipokines, apelin was likely to be involved in the pathophysiology of T2DM and CVD and this could be explained by different mechanisms such as the level of apelin in our obese T2DM patients correlated closely with BMI and the elevated levels may be a result of IR compensatory reaction, However, as the other side of a coin, the apelin may also inhibit the release of insulin, aggravating the disorders of glucose metabolism which was also proved by [43].

Moreover, by coordination with other factors associated with increased circulating free fatty acids, apelin may cause the occurrence of IR [44]. Another explanation was showed by [45] who reported that apelin correlated with oxidative stress and inflammation markers (Ox-LDL and IL-1 β). As important inflammatory factors, they could be involved in the development of atherosclerosis. Thus, understanding the contribution of such an adipokines in obesity-associated disorders appears to be of major importance.

Conclusion

In the face of the current obesity epidemic, the nature of the relationship between obesity and T2D is of great importance. However, it seems that in obese patients such as those suffering from diabetes or CVD, in addition to obesity, the type of illness also affects inflammation or anti-inflammation mediators' levels. The present study indicates that lower concentration of circulating Omentin together with higher concentration of apelin linked with an increase in multiplicity of metabolic risk factors, suggesting that Omentin and apelin serve as beneficial biomarkers for assessment of metabolic risk factors.

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Ethical approval:

The study was approved by the Committee on Medical Ethics of Suez Canal University. The study was carried out in accordance with the regulations and recommendations of the Declaration of Helsinki. (REC number: GH2008H).

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