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# Associations of Serum Omentin and Apelin Concentrations with Obesity, Diabetes Mellitus Type 2 and Cardiovascular Diseases in Egyptian Population

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## Abstract

**Background** and aim: Dysregulation of omentin, a beneficial adipokine and apelin, an inflammatory adipokine, is thought to play a role in the development of type 2 diabetes mellitus and cardiovascular disease. The objective of this study was to evaluate the relationship between circulating omentin and apelin concentrations and components of the metabolic syndrome in adults with and without type 2 diabetes mellitus or cardiovascular disease.

**Methods:** A total of 240 adults sex and age-matched were included in the current case-control study, including 80 healthy non-obese controls, 80 obese patients with T2DM without cardiovascular disease, and 80 obese patients with T2DM with cardiovascular disease . Fasting blood sample was collected to determine biochemical indicators and insulin resistance index (HOMA-IR). Omentin, apelin, interleukin-1β (IL-1β), troponin-T, and oxidized LDL (Ox-LDL) plasma level was assessed by ELISA. Associations of adipokines with biochemical parameters of the patients were determined.

**Results:** Serum omentin levels were significantly lower and serum apelin and IL-1β concentrations were significantly higher in obese diabetic groups compared to non-obese controls. In correlation analyses, omentin negatively associated with the HOMA-IR index, apelin, and troponin-T, whereas apelin was positively associated with IL-1β, BMI, and troponin.

**Conclusions:** Our study supports the hypothesis that abnormal production of omentin and apelin can contribute to the pathogenesis of obesity-related complications including T2DM and cardiovascular disease.

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

## Introduction

Obesity is a chronic multifactorial disease that is associated with numerous metabolic disorders, including Type 2 Diabetes Mellitus (T2DM) [1,2]. 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 adipokine secretion pattern reflects adipose tissue function and seems to be important for determining the individual risk to develop metabolic and cardiovascular comorbidities of obesity [7]. When adipose tissue inflammation and dysfunction have developed, adipokine secretion is significantly changed towards a diabetogenic, pro-inflammatory, and atherogenic pattern [8].

Omentin, apelin, and IL-1β are adipokines that play 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. Recent studies underscore anti-inflammatory, anti-atherogenic, and anti-diabetic properties of omentin [11].

The other newly discovered adipokine is apelin-12, a 12-amino acid peptide, expressed in human adipocytes and 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 apelin concentrations were significantly increased in T2DM patients with or without CVD [14] and positively correlated with serum IL-1β concentrations and negatively associated with serum Triacylglycerols (TAGs) and BMI [15]. Moreover, 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-1β as a pro-inflammatory cytokine was significantly increased and correlated with Troponin-T

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and Ox-LDL in obese diabetic patients [17]. IL-1β has been reported to contribute to β-cell failure and the progression of atherosclerosis as well as heart failure [18]. In the context,of current obesity epidemiology in Egypt The present work aimed to study the association between novel adipokines and obesity and its diabetic and cardiovascular complications in the 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. Participants were classified as having T2DM if they had one or more components of the American Diabetes Association criteria: FPG ≥126 mg/dl (7.0 mmol/l) or 2-h plasma glucose ≥200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water or in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dl (11.1 mmol/l). A patient was considered to have CVD if he had history of myocardial 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 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 nonsmokers. 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 ($m^2$) and subjects with BMI equal or more than 30 $kg/m^2$ were considered as obese subjects and placed in obese diabetic group. The control group was those with BMI lower than 30 $kg/m^2$.

### Biochemical assay

Participants were weighed in a gown and without shoes. Blood pressure was measured with an automated monitor two times after a 5-minute rest period, and the average of the two blood pressures was used in study analyses. 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 Blood 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, Monobind, Inc., USA) with a minimum detectable concentration of 1.76 mlU/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) × 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 (MyoBioSource, Inc., USA) according to manufacturer's instructions (R&D Systems, Wiesbaden, Germany).

**Adipokines determination:** Inflammatory Cytokine; serum IL-1β was measured by ELISA kit (Boaster Biological Technology, Inc., USA) with sensitivity of 6.5 pg/ml [25]. As for novel adipokines; serum omentin levels were measured by ELISA kit (Alpco Diagnostics, Inc., USA) with sensitivity of 0.4 ng/ml [26]. While serum apelin-12 levels 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% [27].

### Statistical analysis

The data are presented as mean ± Standard Deviation (SD). Differences between variables were calculated using the Student's t test. To determine differences between groups, analysis of variance (ANOVA) followed by Bonferroni's post-hoc analysis was used for multiple comparisons between different groups. Pearson's correlations were computed to assess the relationship between variables. All statistical analyses were performed with SPSS, version 17.0 (SPSS Inc.).

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 and their clinical characteristics are given in Table 1. Compared to controls, patients had significantly changed all conventional risk factors for obesity complications, including BMI, hypertension (defined as a systolic Blood Pressure (BP) #140 mmHg, a diastolic BP #90 mmHg, or both), FBG, insulin, HDL, TAG, and TC (P<0.05). In diabetic groups, a significantly higher serum FBG and insulin levels as well as the HOMA-IR values

| Groups | Control | T2DM | T2DM + CVD | *P value* |
|---|---|---|---|---|
| n | 80 | 80 | 80 | |
| Age (years) | 38.6 ± 4.2 | 42 ± 3 | 40.3 ± 2.5 | NS |
| BMI ($Kg/m^2$) | 21 ± 1.7 | 32.4 ± 1.4[a] | 32.6 ± 1.6[a] | 0.01 |
| DM duration (years) | --------- | 3.5 ± 1 | 4.2 ± 0.8 | |
| Systolic blood pressure (mmHg) | 114 ± 10.5 | 133 ± 16.9[a] | 182.6 ± 12.3[a,b] | 0.01 |
| Diastolic blood pressure(mmHg) | 73.4 ± 4.9 | 85.2 ± 8.8[a] | 94.7 ± 10.6[a,b] | 0.01 |
| FBG (mg/ dL) | 100 ± 3.7 | 180 ± 24.6[a] | 182 ± 21.9[a] | 0.01 |
| Insulin (μIU/mL) | 7.6 ± 1.3 | 17.7 ± 3.2[a] | 18.12 ± 3[a] | 0.01 |
| HOMA-I.R index | 1.9 ± 0.3 | 11 ± 1.55[a] | 11.07 ± 1.8[a] | 0.01 |
| TAG (mg/dL) | 129 ± 29 | 280 ± 19 [a] | 284 ± 20.4[a] | 0.01 |
| TC (mg/dL) | 172 ± 16 | 285 ± 32[a] | 290 ± 23[a] | 0.01 |
| HDL (mg/dL) | 38 ± 1.7 | 25.6 ± 2[a] | 27.4 ± 2.1[a] | 0.01 |

T2DM: Type 2 Diabetes Mellitus without Cardiovascular Diseases; T2DM+CVD: Type 2 Diabetes Mellitus with Cardiovascular Diseases; BMI: Body Mass Index; FBG: Fasting Blood Glucose; TAG: Triacylglycerol; TC: Total Cholesterol; HDL: High Density Lipoprotein.
Data is given as mean ± S.D, range. NS=Not Significant.
[a,b]Significant difference from control and T2DM without CVD groups, respectively. *P values* are for the comparison between the control and the study groups.

**Table 1:** General characteristics of the study population.

were observed. In addition there were no significant differences in the baseline characteristics between diabetic patients and controls in terms of age and sex. Regarding cardiovascular makers in Table 2; 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). The Ox-LDL levels were increased by 2.9-fold in the diabetic groups compared to controls (P<0.05). The T2DM+CVD group also showed significantly higher serum troponin-T and Ox-LDL levels compared to the T2DM group (P<0.05). Regarding serum adipokine levels (Table 2), IL-1 β concentrations were increased in the T2DM and T2DM + CVD groups compared to the control group (28.8 ± 2.34 and 29.7 ± 2.1 pg/mL versus 19.17 ± 1.76 pg/mL, respectively; P<0.05). For omentin, there was a significant decrease in its serum levels in both T2DM and T2DM +CVD groups compared to controls (23 ± 4.9 pg/mL and 20.49 ± 5.4 pg/mL versus 58.8 ± 8 pg/mL, respectively; P <0.05). Regarding apelin, its serum levels were increased by 2.5-fold in the T2DM + CVD group compared to controls (P <0.05).

In Pearson's correlation analyses, omentin levels were negatively correlated with insulin (r=-0.92, p=0.001) (Table 3), HOMA-IR (r=-0.89, p=0.001), troponin-T (r=-0.6, p=0.0001) and TC levels (r=-0.87, p=0.0001) (Figure 1). However, apelin levels were negatively correlated with omentin (r=-0.82, p=0.001) (Figure 2) and positively with IL-1# (r=0.8, p=0.001) (Figure 3), troponin–T (r=0.86, p=0.001), BMI (r=0.84, p=0.0001), and TAG (r=0.83, p=0.0001).

| Groups | Control | T2DM T2DM + CVD | | *P value* |
|---|---|---|---|---|
| n | 80 | 80 | 80 | |
| Troponin-T (ng/ml) | 0.008 ± 0.01 | 0.69 ± 0.05[a] | 4.71 ± 1.02[a,b] | 0.01 |
| Ox-LDL (mg/dL) | 1.25 ± 0.35 | 3.1 ± 0.53[a] | 3.73 ± 0.59[a,b] | 0.01 |
| IL-1β (pg/mL) | 19.2 ± 1.6 | 28.8 ± 2.3[a] | 29.7 ± 2.1[a,b] | 0.01 |
| Omentin(pg/mL) | 58.8 ± 8 | 23 ± 4.9[a] | 20.5 ± 5.4[a,b] | 0.01 |
| Apelin (ng/mL) | 0.79 ± 0.07 | 1.79 ± 0.17[a] | 1.99 ± 0.49[a,b] | 0.01 |

IL-1β: Interleukin-1β, Ox-LDL: oxidized LDL.
Data are presented as mean ± S.D, range.
[a,b]Significant difference from control and T2DM without CVD groups, respectively.
*P values* are for the comparison between the control and the study groups at significance level ≤ 0.05.

**Table 2:** Troponin-T, Ox-LDL, IL-1β, Omentin, and Apelin in studied groups

| Variable | Omentin | | Apelin | |
|---|---|---|---|---|
| | *β* | *P* | *β* | *P* |
| Age | -0.235 | NS | 0.168 | NS |
| BMI | -0.449 | NS | 0.44 | <0.001 |
| D.M duration | -0.148 | NS | 0.258 | NS |
| FBG | -0.117 | NS | 0.224 | NS |
| TC | -0.62 | 0.01 | 0.183 | NS |
| TAG | -0.18 | NS | 0.45 | <0.001 |
| HDL-C | 0.464 | NS | -0.229 | NS |
| Insulin | -0.42 | 0.01 | 0.689 | NS |
| HOMA-IR | -0.44 | 0.01 | 0.69 | NS |
| Troponin-T | -0.66 | <0.0001 | 0.67 | <0.0001 |
| Ox-LDL | -0.431 | NS | 0.51 | NS |
| IL-1β | -0.534 | NS | 0.46 | <0.01 |
| Omentin | | | -0.64 | 0.01 |
| Apelin | -0.64 | 0.01 | | |

Evaluated by multiple linear regression models with several levels of adjustment; β: standardized coefficients. NS=not significant.

**Table 3:** Multiple linear regression analysis using either apelin or omentin as dependent variable.

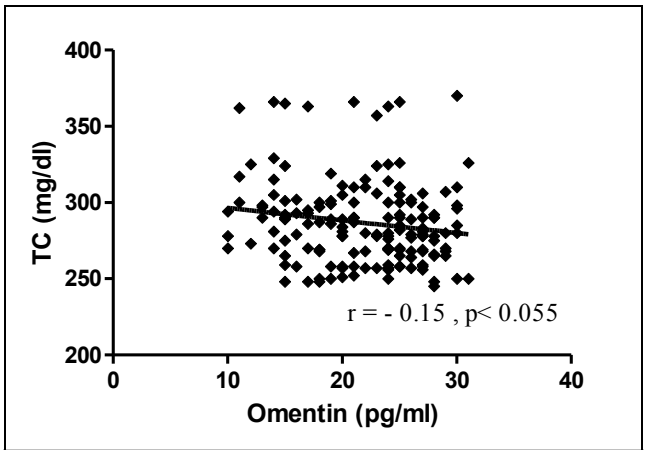


**Figure 1:** Correlation between omentin and Total Cholesterol (TC) in diabetic patients (groups T2DM and T2DM+CVD) (n=160). Each individual value is represented by a symbol (■) *r*=Pearson's correlation coefficients.

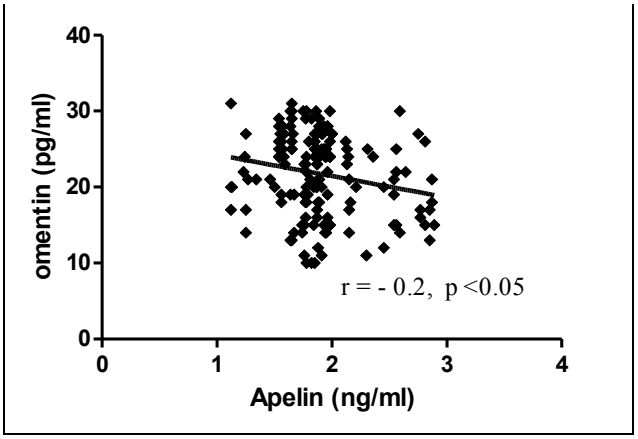


**Figure 2:** Correlation between apelin and omentin in diabetic patients (groups T2DM and T2DM+CVD) (n=160). Each individual value is represented by a symbol (■). *r*=Pearson's correlation coefficients.

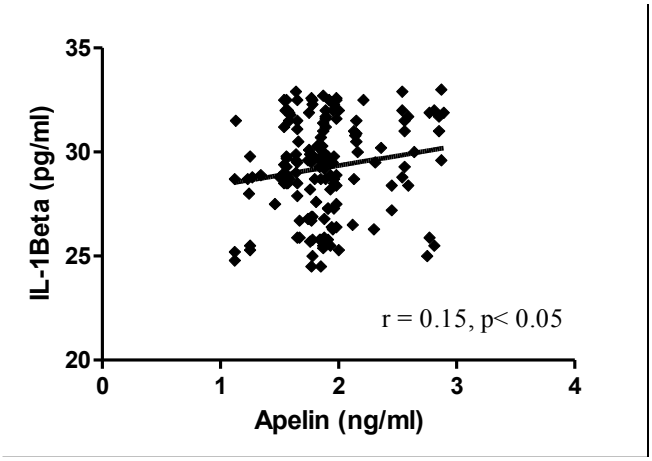


**Figure 3:** Correlation between apelin and IL-1β in diabetic patients (groups T2DM and T2DM + CVD) (n=160). Each individual value is represented by a symbol (■). *r*=Pearson's correlation coefficients.

Multiple regression analysis with all the significant variables confirmed that BMI, TAG, troponin-T, and IL-1β were all determinants of serum apelin levels independently from age, FBG, insulin, and TC (Table 3). While serum omentin levels were dependent on insulin, TC, and troponin-T as well as independent from age, BMI, FBG, and IL-1β.

## 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-1β).

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 Defilippi et al. [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-1β in our population of diabetic patients. A recent study conducted by Manica-Cattani et al. [15] have described a positive association between IL-1β and obesity, suggesting functional effects on fat mass, fat metabolism and body mass. This is supported by the positive correlation found between IL-1β and BMI in our study. However, it is known that adipose tissue can synthesize and release the main pro-inflammatory cytokines; IL-1β 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-1β; this was also supported by Mojtaba et al. [17]. who has shown that IL-1β plays a role in diseases associated with metabolic syndrome such as atherosclerosis and T2DM. In our present study IL-1β was positively correlated with troponin-T and Ox-LDL in our diabetic groups.

According to Ohashi et al. [35] in addition to the effective pro-inflammatory adipokine described above, adipose tissues also secrete a smaller number of anti-inflammatory factors, such as omentin, Omentin is a novel visceral fat depot-specific adipokine 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 Zhong et al. [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 Moreno-Navarrete et al. [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 Yang et al. [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 Ohashi et al. [35] obesity leads to the down-regulation of anti-inflammatory factors, such as omentin and the up-regulation of IL-1β 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, Dray et al. [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-1β 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-1β in the development of IR and atherosclerosis.

Although, apelin has been viewed as a beneficial adipokine up-regulated in obesity as confirmed by Dray et al. [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 Higuchi et al. [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 García-Díaz et al. [45] who reported that apelin correlated with oxidative stress and inflammation markers (Ox-LDL and IL-1β). As important inflammatory factors, they could be involved in the development of atherosclerosis. Thus, understanding the contribution of such an adipokine in obesity-associated disorders appears to be of major importance.

In conclusion, in the context of the current obesity epidemic, the nature of the relationship of obesity with T2DM and CVD is of great importance. However, it seems that diabetes and CVD that often accompany obesity may also affect inflammation or anti-inflammatory mediators. The present study clearly indicates that lower circulating omentin concentration together with higher serum apelin concentration are associated with an increase of numerous metabolic risk factors, suggesting that both adipokines may serve as potential biomarkers for assessment of metabolic risk factors.

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