*Original Article*

# Omentin-1 and its Relation to Arterial Stiffness and Carotid Intima- Media Thickness in Type 2 Diabetic Patients

*Talaat A. Abdel-Fattah, MD[1], Shadya A. Helmy, MD[2], Mohamed M. Rezk, MD[3], Kamel H. Rohoma, MD[1], Sherihan E. Hemida, MBBCh[1].*

*[1]Department of Internal Medicine (Unit of Diabetes & Metabolism), [2]Department of Diagnostic Radiology, [3]Department of Clinical and Chemical Pathology, University of Alexandria, Faculty of Medicine, Alexandria, Egypt.*

## Abstract:

**Purpose:** Atherosclerosis is a major complication of type 2 diabetes mellitus. Omentin-1 is a novel adipokine implicated in body metabolism. Carotid intima media thickness (CIMT) is an established marker for atherosclerosis and a predictor of cardiovascular events. Omentin was found to be reduced in obese subjects and to correlate negatively with BMI, waist circumference and increased CIMT. There are few studies about relation between omentin level and CIMT in diabetics and none of them studied the relation of omentin to the presence of macrovascular complications. That is why we conducted the current research to assess the serum level of omentin-1 in type 2 diabetic subjects versus control and to identify its relationship with atherosclerosis and the presence of macrovascular complications in the diabetic group. **Methods:** This study enrolled 60 subjects divided into three groups. Group (1): included 20 type 2 diabetic patients with history of macrovascular complications, Group (2): included 20 newly diagnosed type 2 diabetic patients without history of macrovascular complications, Group (3): included 20 healthy subjects as control. Assessment included thorough history taking, complete clinical examination, ankle/brachial index, carotid ultrasound, laboratory investigations including metabolic profile and plasma omentin-1 by ELISA. **Results:** Omentin-1 level is significantly lower in subjects with diabetes and macrovascular complications than the newly diagnosed diabetic patients and control group. glycosylated hemoglobin, fasting blood glucose, high sensitive C-reactive protein, body mass index, waist circumference and CIMT have negative correlations with omentin-1 level, while ankle/brachial index is positively correlated. **Conclusions:** Omentin-1 level is lowermost in diabetic patients with macrovascular complications. It is an independent negative predictor of CIMT.

**Keywords:** Omentin-1, Atherosclerosis, Carotid IMT, ankle/brachial index, Diabetes.

## Introduction:

Diabetes Mellitus is a very common metabolic disease occurring in different age groups due to insulin resistance, deficiency or both. It has a rapidly increasing prevalence in both developing and developed countries that is amounting to an epidemic. Whereas 382 million people were diagnosed as diabetics in 2013, it is expected to increase to 592 millions by the year 2035[1].Type 2 diabetes comprises more than 90% of all diabetics worldwide[2].

People with diabetes are at high risk of developing macrovascular complications especially coronary heart disease and stroke, thus becoming the leading cause of mortality and morbidity among these people with nearly 50% of diabetics dying from cardiovascular disease[3]. Atherosclerosis is considered the central pathological mechanism of macrovascular complications. It starts very early and progresses throughout life. Evidence shows that in addition to the classical risk factors like dyslipidemia and dysglycemia, chronic inflammation plays a pivotal role in the development of atherosclerosis[4].

Abdominal obesity is associated with low grade inflammation. A myriad of evidence shows that Obesity, especially of central distribution, has been linked to cardiovascular disease[5,6]. Visceral adipose tissue acts as an endocrine organ secreting bioactive substances, termed adipokines, which regulate adipose tissue function and influence glucose metabolism

and energy balance at the systemic level[7]. Alteration of the level of these adipokines in obese subjects contributes to the development of a chronic inflammatory state that impairs normal adipose tissue function and participates to many adverse outcomes like atherosclerosis[8]. Adipokines demonstrate different properties; some have pro-inflammatory activity thus promoting insulin resistance and atherosclerosis, while others have anti-inflammatory and insulin sensitizing effect and could be considered as "protectors"[9].

Omentin-1 is one of the recently discovered adipokines secreted selectively from omental[10] and epicardial adipose tissue[11]. It is a secretory hydrophilic glycoprotein consisting of 313 amino acids and 1-linked oligosacharides, its basic structural unit is a 120-kDa homotrimer in which 40-kDa polypeptides are bridged by disulfide bonds and it is considered as a new type of Ca2+ -dependent lectin with affinity for galacto-furanosyl residues which are constituents of pathogens and dominant immunogens[12]. A homolog of omentin-1 has been identified that shares 83% amino acid identity with omentin-1 and was referred to as omentin-2, however omentin-1 was shown to be the major circulating isoform in human plasma[12].

Regarding carbohydrate metabolism, Omentin-1 has no effect on basal glucose uptake, however, it enhances insulin-stimulated glucose uptake in adipocytes. Also it increases AKT phosphorylation in the absence and presence of insulin[13].

Recent studies noticed that omentin-1 is involved in many chronic inflammatory processes[14], the defense system against microorganisms[13], iron metabolism[13] and many other diseases including cardiovascular disease[15]. It is found in several recent studies that omentin-1 correlates positively with high-density lipoprotein cholesterol while it is correlates negatively with BMI, waist circumference fasting blood glucose[16,17] and increased intima media thickness IMT[18].

Carotid intima-media thickness [CIMT], a measurement of the tunica intima and tunica media of the carotid, has been frequently used since the mid-1990s as a method of assessment of atherosclerosis. It is done usually by external ultrasound but it can be measured by other methods like internal, invasive ultrasound catheters. IMT is considered an atherosclerotic disease marker in humans, also to track the regression, arrest or progression of atherosclerosis. An IMT greater than 1.1mm is indicative of atherosclerosis and increased risk of cardiovascular disease[19]. In 2010 the American Heart Association and the American College of Cardiology claimed the use of IMT on intermediate risk patients[20].

There are few studies about relation between omentin level and CIMT in diabetics but none of them studied the relation of omentin to the presence of macrovascular complications. That is why we conducted the current research to assess the serum level of omentin-1 in type 2 diabetic subjects versus control and to identify its relationship with atherosclerosis and the presence of macrovascular complications in the diabetic group.

**Subjects and Methods:**

This is a cross-sectional study performed to assess the level of serum omentin-1 and its relationship with atherosclerosis (presented as increased carotid intima media thickness and decreased ankle brachial index) and the presence of macrovascular complications in type 2 diabetic patients. It enrolled 60 subjects selected from outpatient clinics of Alexandria main university hospital and Alexandria Police hospital. The selected subjects were divided into 3 groups. Group (1) included 20 type 2 diabetic subjects with history of one or more macrovascular complications e.g. ischemic heart disease, transient ischemic attack, stroke and peripheral arterial disease (PAD). Group (2) included 20 subjects type 2 newly diagnosed diabetic patients without history of macrovascular complications. Group (3) comprises 20 healthy subjects of matched age and sex as a control.

The study was performed according to the guidelines of the Helsinki Declaration and

approved by the Ethics Committee of the Faculty of Medicine- Alexandria University. All participants who freely accepted to participate in the study were given a patient information sheet and signed a written informed consent.

Subjects with peripheral vascular disease due to causes other than diabetes, known history of coronary heart disease without diabetes, severe uncontrolled hypertension, severe cardiac decompensation, end stage renal disease, Familial hypercholesterolemia, Connective tissue diseases and vasculitis were excluded from this study.

All participants were subjected to the following:

- **Thorough history taking** by a physician including an interview questionnaire covering the following items:
- History of diabetes (type, duration, medications).
- History of macrovascular complications
- History of associated other risk factors (hypertension, dyslipidemia, smoking, family history of DM, hypertension, dyslipidemia, cardiovascular disease and obesity).
- Physical examination:
- Anthropometrics measurements e.g. weight, height, body mass index (BMI), waist circumference and Waist/hip (W/H) ratio.
- Vital signs (heart rate, systolic and diastolic blood pressure).
- Vascular assessment.

- **Ankle/brachial index (ABI):**

We estimate the systolic blood pressure in the two brachial arteries and also the systolic blood pressure in posterior tibial arteries and dorsalis pedis arteries in both lower limbs by inflation of the 30-40 cm cuff then deflating it gradually till appearance of wave on the continous wave Doppler device. According to higher ankle pressure (HAP) method; ABI is calculated as followed:

ABI= the higher of the ankle arterial SBP / the higher of the two brachial SBP[21].

- **Doppler Carotid Artery to determine the carotid intima media thickness**:[22].

Ultrasonographic scanning of the carotid arteries was performed using Philips ClearVue 350 at a transducer frequency of 7-12 MHz at Radiology Department, Alexandria Main University Hospital. Extracranial carotid arteries in the neck were scanned bilaterally in the longitudinal and in the transverse plane. This provided images of the common carotid artery, the carotid bulb, and parts of the internal and external carotid arteries. Scanning was performed by a single experienced ultrasonographer.

Carotid IMT was defined as the distance from the leading edge of the first echogenic line to the leading edge of the second echogenic line on the scans, with the first line representing the lumen–intimal interface and the second line representing the collagen-containing upper layer of the adventitia. The site with the greatest thickness in the longitudinal plane was detected along the vessel from the common carotid artery to the internal carotid artery bilaterally.

- **Laboratory investigations:**

Venous blood samples were obtained after an overnight fasting; another sample was obtained 2 hours postprandial for PPBG measurement. All fasting blood samples were divided into two aliquots: the first part was collected in vacutainer tube containing Na2EDTA for the assay of HbA1C; the second was collected in plain vacutainer tube and centrifuged (3000 rpm) for serum preparation. Serum was used for measuring total cholesterol, TG, LDL-c, HDL-c, glucose, urea, creatinine, hs-CRP and omentin. Serum samples for omentin assay were kept at -80°C till being assayed. Serum omentin-1 concentration was measured using Human Enzyme-linked immunosorbent assay (ELISA) kits (AVISCERA BIOSCIENCE INC, Santa Clara, CA, USA). Serum samples for omentin were diluted and assayed according to manufacturer instructions. All samples were measured in Alexandria Main University Hospital Laboratory.

- Fasting plasma glucose [23].
- Blood Urea and serum creatinine [24].
- Glycated heamoglobin (HbA1c) [23].

- Total serum cholesterol [25].
- High density lipoprotein cholesterol (HDL- Cholesterol) [25].
- Low density lipoprotein cholesterol (LDL- Cholesterol) [25].
- Serum triglycerides [25].
- High sensitivity CRP (hs-CRP) [26].
- Plasma level of omentin-1 by ELISA [27].

**Statistical analysis of the data: [28]**

Data were analyzed using IBM SPSS software package version 20.0. Qualitative data were described using number and percent. Quantitative data were described using mean and standard deviation for normally distributed data while abnormally distributed data was expressed using median, minimum and maximum. Comparison between different groups regarding categorical variables was tested using Chi-square test. For abnormally distributed data, Mann-Whitney Test was used to analyze two independent populations. If more than two populations were analyzed Kruskal Wallis test to be used. Correlations between two quantitative variables were assessed using Spearman coefficient. For normally distributed data, comparison between the three studied groups were analyzed using F-test (ANOVA) and Post Hoc test (Scheffe) for pair-wise comparisons, Significance of the obtained results was judged at the 5% level.

## Results:

Demographic and clinical characteristics of the study subjects are summarized in table (I) that showed no significant difference between the three groups regarding age, sex, exercise and smoking habits. However, There was significant difference regarding DM duration ($p<0.001$), history of hypertension and dyslipidemia ($p<0.001$), weight ($p<0.001$), BMI ($p<0.001$), waist circumference ($p<0.001$), W/H ratio ($p<0.001$), systolic BP ($p=0.041$), heart rate ($p=0.015$) and ankle brachial index (ABI) ($p<0.001$). Also, there was a significant difference ($p<0.05$) between diabetics with history of macrovascular complications versus newly diagnosed diabetics without history of macrovascular complications regarding diabetes duration, history of hypertension, BMI, W/H ratio and ABI. Moreover, there was a significant difference ($p<0.05$) between newly diagnosed diabetics without history of macrovascular complications versus controls regarding ABI and also regarding BMI, history of dyslipidemia and history of hypertension.

Different laboratory findings in addition to the Carotid intima media thickness (CIMT) measurements are summarized in table (II). There was significant difference between the studied groups regarding omentin-1($p<0.001$), CIMT ($p<0.001$), hs-CRP ($p<0.001$), FPG ($p<0.001$), PPPG ($p<0.001$), HbA1c ($p<0.001$), total cholesterol ($p<0.001$), LDL-c ($p<0.001$), HDL-c ($p=0.002$), TG ($p<0.001$) and creatinine ($p=0.031$).

Omentin-1 was significantly lower in diabetics with history of macrovascular complications than in newly diagnosed diabetics without history of macrovascular complications ($p<0.05$) and significantly lower in the later group compared to control ($p< 0.05$). Conversely, CIMT and CRP were significantly higher in diabetics with history of macrovascular disease versus those without ($p<0.05$), and still higher in the later group than control ($p< 0.05$).

As shown in table (III),(IV) in all diabetics, omentin-1 correlated negatively with CIMT, BMI, HbA1c, FPG, PPPG, total cholesterol, LDL-c, TG, hs-CRP and W/H ratio, yet correlated positively with ABI. Regarding CIMT, it correlated negatively, in all diabetics, with omentin-1 level and ABI, while correlated positively with BMI, HbA1c, FPG, PPPG, total cholesterol, LDL-c, TG, hs-CRP and W/H ratio.

In Multivariate linear regression analysis using Omentin-1 as dependent variable, CIMT and HbA1C were the independent predictors; Table (V), while on using CIMT as the dependent variable, omentin-1 was the only independent predictor; Table (VI).

As shown in figure (1): omentin-1 level correlates negatively with carotid intima-media thickness (CIMT) in all diabetic patients.

**Table (I):** Comparison between the study groups according to demographic and clinical data

| | DM cases | | | |
|---|---|---|---|---|
| | **With history of macrovascular complications (n=20)** | **Newly diagnosed without history macrovascular complications (n=20)** | **Control (n=20)** | **p** |
| **Sex (male/female)** | | | | |
| Male | 13 (65%) | 14 (70%) | 15 (75%) | 0.788 |
| Female | 7 (35%) | 6 (30%) | 5 (25%) | |
| **Age (years)** | 56.15 ± 6.98 | 55.25 ± 5.58 | 53.70 ± 4.26 | 0.397 |
| **DM duration (years)** | 11.5 †∂ (0.5 - 31) | 2† (0.25 - 5) | 0 (0 – 0) | <0.001* |
| **History Hypertension** | 20 †∂ (100%) | 15† (75%) | 0 (0%) | <0.001* |
| **History dyslipidemia** | 19 † (95%) | 19† (95%) | 0 (0%) | <0.001* |
| **Exercise** | 5† (25%) | 10 (50%) | 12 (60%) | 0.072 |
| **Smoking** | 8 (40%) | 10 (50%) | 10 (50%) | 0.765 |
| **Weight (kg)** | 96.25† ± 12.87 | 88.70 ± 9.39 | 81.65 ± 6.23 | <0.001* |
| **Height (m)** | 1.78 ± 0.08 | 1.80 ± 0.07 | 10.83 ± 0.06 | 0.176 |
| **BMI (kg/m2)** | 30.23†∂ ± 2.82 | 27.46† ± 2.13 | 24.44 ± 1.50 | <0.001* |
| **Waist Circumference (cm)** | 97.55† ± 8.48 | 91.55 ± 6.19 | 91.55 ± 3.56 | <0.001* |
| **Hip Circumference (cm)** | 97.95 ± 5.80 | 96.45 ± 5.84 | 96.50 ± 3.25 | 0.577 |
| **W/H ratio** | 0.99†∂ ± 0.05 | 0.95 ± 0.02 | 0.94 ± 0.01 | <0.001* |
| **Systolic BP (mmHg)** | 138.50† ± 10.40 | 134.50 ± 12.34 | 129.75 ± 8.96 | 0.041* |
| **Diastolic BP (mmHg)** | 90.0 ± 12.14 | 86.50 ± 11.37 | 81.75 ± 7.48 | 0.053 |
| **HR (beat/minute)** | 75.0† ± 8.60 | 77.20 ± 8.52 | 82.20 ± 5.87 | 0.015* |
| **ABI** | 0.48†∂ ± 0.13 | 0.81† ± 0.11 | 1.10 ± 0.15 | <0.001* |

Values was expressed as (mean ± SD) for normally distributed parameters, median (Min. – Max.) for abnormally distributed parameters and percentage for qualitative values

†: Significant difference (p<0.05); diabetics (with or without history of macrovascular complications) versus control

*∂*: Significant difference (p<0.05); diabetics with history of macrovascular complications versus newly diagnosed diabetics without history of macrovascular complications

*: Statistically significant at p ≤ 0.05

BMI: body mass index, W/H ratio: waist/hip ratio, ABI: ankle brachial index.

**Table (II):** Comparison between the studied groups according to laboratory investigations and CIMT

| | DM | | | |
|---|---|---|---|---|
| | **With history macrovascular complications (n=20)** | **Newly diagnosed without history macrovascular complications (n=20)** | **Control (n=20)** | **p** |
| **Omentin-1 (ng/L)** | 1105†∂(1078–1218) | 1355†(122-1428) | 1561 (1428–6866) | <0.001* |
| **CIMT (mm)** | 1.56†∂ ± 0.18 | 1.03† ± 0.21 | 0.67 ± 0.12 | <0.001* |
| **Hs-CRP (mg/L)** | 7.31†∂ ± 0.93 | 4.17† ± 0.67 | 1.59 ± 0.70 | <0.001* |
| **FPG (mg/dl)** | 222.1†∂ ± 43.21 | 145.1† ± 10.95 | 82.05 ± 8.21 | <0.001* |
| **PPPG (mg/dl)** | 330.5†∂ ± 56.44 | 180.40† ± 11.89 | 115.20 ± 12.59 | <0.001* |
| **HbA1c (%)** | 10.10†∂ ± 1.13 | 7.62† ± 0.72 | 5.09 ± 0.40 | <0.001* |
| **Urea (mg/dl)** | 42.80 ± 5.04 | 41.60 ± 4.77 | 40.35 ± 3.57 | 0.237 |
| **Creatinine (mg/dl)** | 1.0 ± 0.23 | 0.99 ± 0.19 | 0.85 ± 0.17 | 0.031* |
| **Total Cholesterol (mg/dl)** | 331.8†∂ ± 46.45 | 232.05† ± 41.20 | 188.05 ± 7.44 | <0.001* |
| **LDL-c (mg/dl)** | 243.35†∂ ± 42.94 | 158.8† ± 36.02 | 109.45 ± 8.07 | <0.001* |
| **HDL-c (mg/dl)** | 37.9 † ± 8.60 | 38.4† ± 8.19 | 45.55 ± 3.73 | 0.002* |
| **TG (mg/dl)** | 253.2†∂ ± 23.57 | 185.05† ± 16.09 | 142.0 ± 6.75 | <0.001* |

Values was expressed as (mean ± SD) for normally distributed parameters or median (Min. – Max.) for abnormally distributed parameters

†: Significant difference (p < 0.05); diabetics (with or without history of macrovascular complications) versus control

*∂*: Significant difference (p < 0.05); diabetics with history of macrovascular complications versus newly diagnosed diabetics without history of macrovascular complications

*: Statistically significant at p ≤ 0.05

CIMT: carotid intima media thickness, Hs-CRP: high sensitivity C reactive protein, FPG: fasting plasma glucose, PPPG: postprandial plasma glucose, LDL-c: low-density lipoprotein cholesterol, HDL-c: high density lipoprotein cholesterol. TG: triglycerides.

**Table (III):** Correlation between Omentin-1 and different clinical and laboratory parameters in each group

| | DM | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | With history macrovascular complications (n=20) | | Newly diagnosed without history macrovascular complications (n=20) | | Control (n=20) | | All diabetics | |
| | $r_s$ | P | $r_s$ | P | $r_s$ | p | $r_s$ | p |
| **CIMT (mm)** | -0.587* | 0.007 | -0.738* | <0.001 | 0.077 | 0.746 | -0.902* | <0.001 |
| **ABI** | 0.576* | 0.008 | 0.568* | 0.009 | -0.219 | 0.354 | 0.881* | <0.001 |
| **Waist circumference (cm)** | 0.248 | 0.291 | -0.424 | 0.062 | 0.046 | 0.847 | -0.311 | 0.051 |
| **W/H ratio** | -0.113 | 0.634 | -0.349 | 0.132 | -0.033 | 0.891 | -0.450* | 0.004 |
| **BMI (kg/m$^2$)** | 0.195 | 0.410 | -0.313 | 0.178 | 0.291 | 0.214 | -0.462* | 0.003 |
| **Systolic BP (mmHg)** | 0.390 | 0.089 | -0.196 | 0.408 | -0.148 | 0.534 | -0.052 | 0.743 |
| **Diastolic BP(mmHg)** | 0.207 | 0.382 | -0.299 | 0.200 | -0.014 | 0.952 | -0.151 | 0.352 |
| **Heart rate( beat/min)** | 0.234 | 0.321 | -0.094 | 0.694 | 0.293 | 0.210 | 0.158 | 0.331 |
| **HbA1C (%)** | -0.590* | 0.006 | -0.444* | 0.050 | -0.041 | 0.865 | -0.864* | <0.001 |
| **FPG (mg/dl)** | -0.560* | 0.010 | -0.588* | 0.006 | 0.258 | 0.272 | -0.877* | <0.001 |
| **PPPG (mg/dl)** | -0.546* | 0.013 | -0.415 | 0.069 | 0.224 | 0.342 | -0.870* | <0.001 |
| **Urea (mg/dl)** | -0.304 | 0.193 | 0.035 | 0.885 | -0.280 | 0.231 | -0.191 | 0.238 |
| **Creatinine (mg/dl)** | 0.149 | 0.530 | -0.102 | 0.669 | 0.071 | 0.766 | -0.016 | 0.924 |
| **Total cholesterol (mg/dl)** | -0.074 | 0.757 | -0.558* | 0.006 | 0.135 | 0.571 | -0.748* | <0.001 |
| **LDL-c (mg/dl)** | -0.164 | 0.489 | -0.609* | 0.004 | 0.194 | 0.412 | -0.765* | <0.001 |
| **HDL-c (mg/dl)** | -0.123 | 0.606 | 0.132 | 0.580 | 0.465* | 0.039 | 0.074 | 0.650 |
| **TG (mg/dl)** | -0.467* | 0.038 | -0.235 | 0.318 | -0.103 | 0.665 | -0.838* | <0.001 |
| **Hs-CRP (mg/L)** | -0.789* | <0.001 | -0.322 | 0.166 | 0.201 | 0.396 | -0.889* | <0.001 |

rs: Spearman coefficient

*: Statistically significant at p ≤ 0.05

CIMT: carotid intima media thickness, ABI: ankle brachial index, BMI: body mass index, W/H ratio: waist/hip ratio, FPG: fasting plasma glucose, PPPG: postprandial plasma glucose, LDL-c: low-density lipoprotein cholesterol, HDL-c: high density lipoprotein cholesterol. TG: triglycerides, Hs-CRP: high sensitivity C reactive protein.

**Table (IV):** Correlation between CIMT and different clinical and laboratory parameters in each group

| | DM | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | With history macrovascular complications (n=20) | | Newly diagnosed without history macrovascular complications (n=20) | | Control (n=20) | | All diabetics | |
| | $r_s$ | P | $r_s$ | p | $r_s$ | p | $r_s$ | P |
| **Omentin-1 (ng/L)** | -0.587* | 0.007* | -0.738* | <0.001* | 0.077 | 0.746 | -0.902* | <0.001* |
| **ABI** | -0.479* | 0.033* | -0.547* | 0.013* | -0.225 | 0.341 | -0.853* | <0.001* |
| **Waist circumference (cm)** | -0.230 | 0.329 | 0.240 | 0.308 | 0.151 | 0.525 | 0.281 | 0.079 |
| **W/H ratio** | -0.112 | 0.639 | 0.200 | 0.399 | -0.098 | 0.682 | 0.375* | 0.017* |
| **BMI (kg/m$^2$)** | -0.230 | 0.329 | 0.032 | 0.894 | 0.269 | 0.251 | 0.364* | 0.021* |
| **Systolic BP (mmHg)** | -0.003 | 0.989 | 0.322 | 0.167 | 0.200 | 0.398 | 0.206 | 0.203 |
| **Diastolic BP(mmHg)** | -0.085 | 0.721 | 0.348 | 0.133 | -0.052 | 0.826 | 0.206 | 0.201 |
| **Heart rate (beat/min)** | -0.208 | 0.380 | -0.052 | 0.827 | 0.256 | 0.276 | -0.184 | 0.256 |
| **Creatinine (mg/dl)** | -0.039 | 0.869 | 0.171 | 0.472 | 0.191 | 0.419 | 0.047 | 0.776 |
| **Total cholesterol (mg/dl)** | 0.293 | 0.210 | 0.469* | 0.037* | 0.196 | 0.409 | 0.748* | <0.001* |
| **LDL-c (mg/dl)** | 0.346 | 0.136 | 0.523* | 0.018* | 0.349 | 0.132 | 0.761* | <0.001* |
| **HDL-c (mg/dl)** | 0.311 | 0.182 | -0.211 | 0.372 | 0.0 | 1.000 | -0.010 | 0.953 |
| **TG (mg/dl)** | 0.055 | 0.819 | 0.474* | 0.035* | -0.139 | 0.560 | 0.791* | <0.001* |
| **Hs CRP (mg/L)** | 0.485* | 0.030* | 0.523* | 0.018* | -0.219 | 0.353 | 0.854* | <0.001* |

rs: Spearman coefficient

*: Statistically significant at p ≤ 0.05

CIMT: carotid intima media thickness, ABI: ankle brachial index, BMI: body mass index, W/H ratio: waist/hip ratio, FPG: fasting plasma glucose, PPPG: postprandial plasma glucose, LDL-c: low-density lipoprotein cholesterol, HDL-c: high density lipoprotein cholesterol. TG: triglycerides, Hs-CRP: high sensitivity C reactive protein.

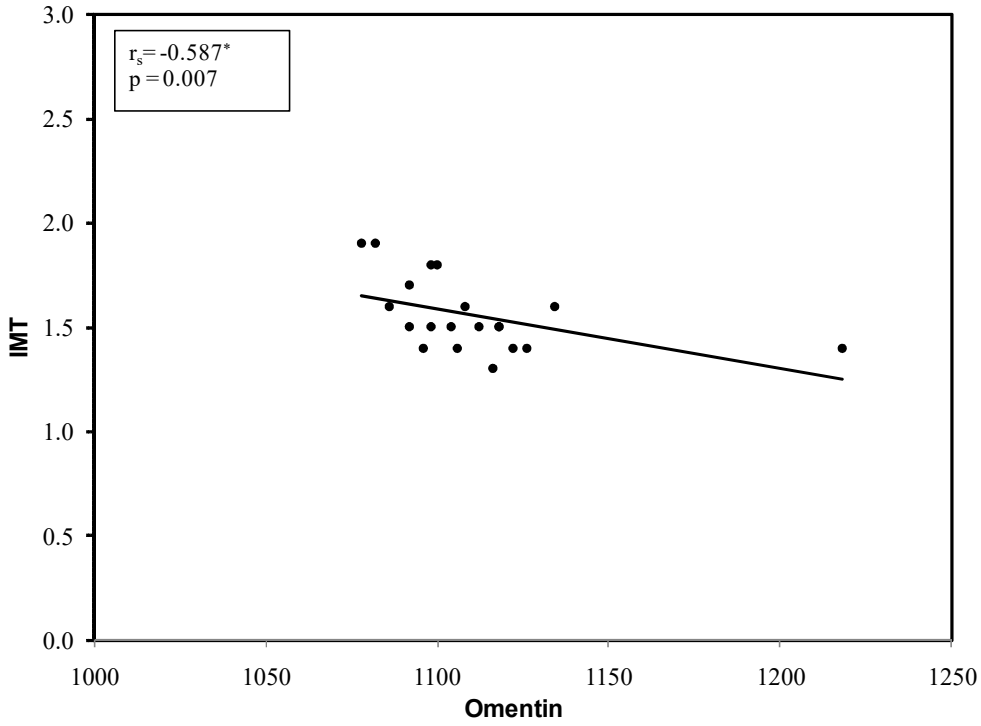


**Figure (1):** Correlation between Omentin with IMT

$r_s$: Spearman coefficient

*: Statistically significant at p ≤ 0.05

**Table (V):** Multivariate linear regression analysis of variables associated with Omentin-1 levels

| | B | SE | t | p |
|---|---|---|---|---|
| **CIMT** | -140.01 | 45.37 | 3.086* | 0.005* |
| **ABI** | -23.467 | 87.41 | 0.268 | 0.790 |
| **BMI** | -1.237 | 3.75 | 0.330 | 0.744 |
| **W/H ratio** | -288.92 | 224.72 | 1.286 | 0.209 |
| **HbA1C** | -27.92 | 13.5 | 2.067* | 0.048* |
| **FPG** | 0.820 | 0.52 | 1.577 | 0.126 |
| **PPPG** | -0.459 | 0.34 | 1.361 | 0.184 |
| **Total cholesterol** | -0.497 | 0.58 | 0.862 | 0.396 |
| **LDL-c** | 0.216 | 0.70 | 0.311 | 0.758 |
| **TG** | -0.293 | 0.42 | 0.697 | 0.491 |
| **Hs CRP** | -2.115 | 15.11 | 0.140 | 0.890 |
| **R = 0.957, $R^2$ = 0.916, F = 27.744*,p <0.001*** | | | | |

B: Unstandardized Coefficients, SE: Standard error, t: t-test of significance, R: coefficient or regression, R2: coefficient or regression, F: F test (ANOVA), *: Statistically significant at p ≤ 0.05, CIMT: carotid intima media thickness, ABI: ankle brachial index, BMI: body mass index, W/H ratio: waist/hip ratio, FPG: fasting plasma glucose, PPPG: postprandial plasma glucose, LDL-c: low-density lipoprotein cholesterol, HDL-c: high density lipoprotein cholesterol. TG: triglycerides, Hs-CRP: high sensitivity C reactive protein.

**Table (VI):** Multivariate linear regression analysis of variables associated with CIMT

| | B | SE | t | p |
|---|---|---|---|---|
| **Omentin-1** | -0.002 | 0.001 | 3.232* | 0.003* |
| **Ankle brachial index** | -0.506 | 0.295 | 1.716 | 0.097 |
| **BMI** | -0.019 | 0.013 | 1.467 | 0.153 |
| **W/H ratio** | -0.051 | 0.818 | 0.062 | 0.951 |
| **HbA1C** | -0.057 | 0.049 | 1.163 | 0.254 |
| **FPG** | 0.001 | 0.002 | 0.389 | 0.700 |
| **PPPG** | 0.000 | 0.001 | 0.265 | 0.793 |
| **LDL-c** | 0.000 | 0.001 | 0.267 | 0.791 |
| **TG** | 0.000 | 0.001 | 0.168 | 0.868 |
| **Hs-CRP** | 0.034 | 0.053 | 0.636 | 0.530 |
| **R = 0.920, $R^2$ = 0.847, F = 16.021*,p <0.001*** | | | | |

B: Unstandardized Coefficients, SE: Standard error, t: t-test of significance, R: coefficient or regression, R2: coefficient or regression, F: F test (ANOVA), *: Statistically significant at p ≤ 0.05, CIMT: carotid intima media thickness, ABI: ankle brachial index, BMI: body mass index, W/H ratio: waist/hip ratio, FPG: fasting plasma glucose, PPPG: postprandial plasma glucose, LDL-c: low-density lipoprotein cholesterol, HDL-c: high density lipoprotein cholesterol. TG: triglycerides, Hs-CRP: high sensitivity C reactive protein.

## Discussion:

The relationship between DM and atherosclerotic diseases is well established[29]. That is why diabetes is considered a cardiovascular disease[30]. Adipokines are implicated in several body functions including cardiovascular functions[31] and insulin resistance[32]; this could be triggered through obesity induced inflammation and signaling pathways[33]. An abundance of adipokines has been associated with development of atherosclerosis and cardiovascular diseases, while others could be protective[34-37]. Omentin-1, also named intelectin-1, is a secretory protein newly identified in 2005. It is selectively expressed in visceral adipose tissue[36]. It was found that decreased omentin-1 levels are associated with increasing obesity and insulin resistance in human body. The combination of obesity and diabetes mellitus, the so-called ‘‘diabesity’’, is increasing the risk of cardiovascular complications[15].

Our study showed that serum omentin-1 level in newly diagnosed diabetics without history of macrovascular complications is significantly lower than the control group and it is much lower in diabetics with history of macrovascular complications. This is in agreement with Pan et al.[38] who found that serum omentin-1 levels were decreased in subjects with impaired glucose regulation. Moreover, this is consistent with Zhang et al.[39] who demonstrated that serum omentin-1 levels significantly decreased in type 2 diabetes patients compared to normal controls. Our results are also supported by a study done by Yoo et al.[40] that rev ealed that serum omentin-1 levels were significantly decreased in type 2 diabetes patients than control.

We also noticed that omentin-1 level was inversely correlated with HbA1c. This is in agreement with Gursoy et al.[41] and Kilic et al. [42] It was demonstrated that recombinant omentin enhanced the uptake of glucose in isolated adipocytes and dramatically increased the insulin induction of Akt/PKB phosphorylation[13]. Pan et al. speculated that decreased serum omentin-1 levels observed in Type 2 diabetes might cause a reduction of insulin-stimulated glucose uptake in visceral and subcutaneous adipocytes or other insulin-sensitive tissue[38]. Moreover, Tan et al.[43] showed that plasma glucose and insulin levels could regulate omentin-1 synthesis directly or indirectly. Again, these facts can elucidate the negative correlation, observed in our study, between

HbA1c and Omentin-1, which was maintained in the multivariate analysis.

In the current study, we demonstrated that omentin-1 is negatively correlated with CIMT in both diabetics and controls. In conformity with our results, Liu et al.[44] showed that omentin-1 was inversely correlated with CIMT in subjects with metabolic syndrome. Moreover, Shibata et al.[18] proved that Circulating omentin-1 levels correlated negatively with max-CIMT and mean-CIMT in 100 apparently healthy Japanese men. In addition, Yoo et al. showed that low circulating omentin-1 was proved as an independent determinant of carotid plaque existence among type 2 diabetic patients[40] as it was reduced in type 2 diabetes patients with carotid plaque compared to those without.

In harmony with the above mentioned studies, Shang et al.[45] demonstrated that serum omentin-1 levels were inversely associated with the presence and angiographic severity of CAD in Metabolic Syndrome patients and that serum omentin-1 might be a potential biomarker to predict the development and progression of CAD in such a cohort of patients. This was supported by Liu et al.[44] who showed that levels of omentin-1 were lower in Metabolic Syndrome than in controls and reduced further in [metabolic syndrome and atherosclerosis] compared with [metabolic syndrome without atherosclerosis].

In contrast to our results, only one recent study has shown that elevated omentin-1 is a strong predictor of cardiovascular events independently from the presence and extent of baseline CAD[46]. On the other hand, Kadoglou et al.[47] showed that low omentin-1 level was positively associated with either low carotid plaque echogenicity index score [GSM score] or carotid-related symptoms; but not after multivariate analysis. They recommended that further investigations were required to study the association of low serum omentin-1 with carotid plaque echolucency.

From our data, ankle/brachial index was positively correlated with circulating omentin-1 level in diabetic patients, however, this was not maintained in the multivariate analysis. This came in consistency with both Yoo et al.[40] who confirmed the positive correlation between omentin and ankle /brachial index after studying the impact of circulating omentin-1 level on arterial stiffening in patients with type 2 diabetes mellitus. Also Bubenek et al.[48] found that ankle/brachial index was significantly correlated positively with omentin-1 during analyzing the results of their study which was performed to assess the gene expression of omentin in peripheral occlusive arterial disease patients .

In this study, we showed that hs-CRP was negatively correlated with serum omentin-1 level in the study groups. This finding came in consistency with results from Tan et al.[15] and Yilmaz et al.[49] studies. Moreover, Moreno-Navarrete et al.[50] demonstrated a negative association between omentin and circulating IL-6 and CRP; both of them are related endothelial dysfunction and atherosclerosis.

A vasodilator effect of omentin-1 was detected on isolated blood vessels. It is suggested that omentin-1 directly induces endothelium-dependent vasodilatation, mediated via endothelium- produced nitric oxide [NO], as it promotes activation of the Akt signaling pathway, modulating the function of NO synthase in the endothelium[51]. It is also reported that omentin suppresses TNF-α stimulated cyclooxygenase-2 expression in cultured endothelial cells through its ability to reduce c-Jun N-terminal kinase activation, thus modulates vascular inflammatory state[52]. Moreover, it was shown that circulating omentin contributed independently to the variance of endothelium-dependent vasodilatation after controlling for age and CRP in subjects with impaired glucose tolerance[51].

In addition, Omentin-1 causes inhibition of endothelial ICAM-1 and VCAM-1 expression via interruption of NF-Kß signaling pathway and suppression of adhesion of monocytes to TNF-α activated endothelial cells[53]. Recently, Xie et al.[54] investigated the effects of omentin-1 on arterial calcification and bone metabolism in vivo and concluded that omentin-1 ameliorates arterial calcification and bone loss in vivo through the regulation of the RANK signaling pathway. All these actions at the molecular level help us explain our results that presume a protective role for omentin-1 against atherosclerosis.

Our results showed also that plasma omentin-1 levels were inversely correlated with BMI and waist circumference. In other words, decreased omentin-1 levels were associated with increasing general and central obesity. These findings are in congruence with the results published by de Souza Batista et al. [16] and Moreno-Navarrete et al.[17] Also, Cai et al.[55] found that the omentin-1 mRNA was negatively correlated with body weight, WHR and BMI.

Another finding in our study that omentin-1 was inversely correlated with total cholesterol, LDL-c and TG. Similarly, in a study done by Saremi et al.[56], there were inverse correlations between omentin-1 and each of total cholesterol and triglyceride. Consonant with this, Shibata et al.[18] showed that Plasma levels of omentin-1 correlated negatively with total cholesterol levels.

**Conclusions and Limitations:**

Omentin-1 level is significantly lower in diabetic patients with macrovascular complications than newly diagnosed diabetics without complications and the controls. Omentin-1 is an independent negative predictor of CIMT, and thus could be considered as an indicator for atherosclerosis. HbA1c and CIMT are the independent factors that negatively influence serum omentin-1 level. This study results are is limited by its cross-sectional design and the relatively small number of subjects.

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