# Visfatin and adiponectin as early markers of atherosclerosis in type 2 diabetes mellitus

Ibtissam Zakaria[a], Mary N. Rizk[a], Maha Rakha[a] and Amal Shehaby[b]

Departments of [a]Internal Medicine and [b]Biochemistry, Cairo University, Cairo, Egypt

Correspondence to Mary N. Rizk, MD, PhD, Department of Internal Medicine, Cairo University, 26 st.18 Mokattam, Cairo, Egypt
Tel: +20 122 398 0137;
e-mail: mnrizk1970@hotmail.com

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**Introduction**

As cardiovascular disease is the leading cause of mortality in type 2 diabetes mellitus, new markers for early detection and risk stratification of diabetic macroangiopathy and microangiopathy are highly desired. Adipocytokines were considered to lead to an increased risk of vascular complications in patients with type 2 diabetes by modulating vascular function and affecting the inflammatory process, thus enhancing atherosclerosis. Two of these were of particular interest, namely, visfatin and adiponectin.

**Aim**

The aim of this study was to evaluate serum visfatin, serum, and urinary adiponectin as early, sensitive surrogate markers of vascular atherosclerosis. We also correlated the levels of these markers to the degree of carotid intimal medial thickness (reflecting the atherosclerotic burden) in type 2 diabetic patients.

**Results**

Sixty diabetic patients were subdivided into two groups: group I (30 patients with carotid atherosclerosis as assessed by carotid Doppler) and group II (30 patients without carotid atherosclerosis). Twenty healthy volunteers participated as controls. Serum visfatin as well as serum and urinary adiponectin were assessed in all the study groups. We found significantly higher levels of serum visfatin among diabetics compared with the control group. Visfatin was also significantly higher in group I diabetics with atherosclerosis than those without ($P<0.05$). Similarly, urinary adiponectin was significantly higher in group I than in group II and in diabetics than in the control group. Serum adiponectin was higher in the control group than both the study groups. Using a regression model, visfatin proved to be the only significant predictor in the model ($\beta=0.03$, $P<0.001$). In fact, visfatin alone proved significant, explaining 63% of the variability in carotid intima-media thickness ($P<0.001$).

**Conclusion**

Serum visfatin is highly correlated with macrovascular complications in diabetic patients. Serum visfatin may emerge as a valuable and cheaper surrogate marker for the prediction of prevalent macrovascular complications in a type 2 diabetic population. It is a novel and easy-to-obtain method for the clinical assessment of vascular stress and cardiovascular disease risk in type 2 diabetes. Future prospective studies are needed to confirm our results.

**Keywords:**
atherosclerosis, type 2 diabetes mellitus, visfatin

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## Introduction

Cardiovascular disease (CVD) is one of the leading causes of morbidity and mortality in type 2 diabetic patients and early detection of macrovascular alterations is of paramount importance for the primary and secondary prevention of CVD and monitoring of optimal medical treatment [1]. There is an interest in identifying markers of subclinical atherosclerosis in order to facilitate earlier diagnosis. Several measures have been used to allow risk stratification of diabetic macroangiopathy and progression of atherosclerosis. Noninvasive measurements of surrogate markers of atherosclerosis, such as carotid intima-media thickness (CIMT) [2], can be helpful in the detection of subclinical diseases, especially among individuals at the highest cardiovascular risk, and for determination of the intensity of pharmaceutical treatment. However, over the past few years, there has been a trend toward the measurement of a number of inflammatory and metabolic markers, which may provide an indirect indicator of vascular damage, hence replacing radiological procedures as more readily available and cheaper modalities. Although many studies [3,4] have addressed this point, the most accurate and more importantly cost-effective marker(s) are yet to be determined.

Recently, diabetes-related adiposity was correlated with multiple cardiometabolic risk factors through altered secretion of adipocytokines and exacerbation of insulin

resistance [5,6]. Adipocytokines were considered to lead to an increased risk of vascular complications in patients with type 2 diabetes by modulating vascular function and affecting the inflammatory process, thus enhancing atherosclerosis [7,8]. Two adipocytokines were major players, namely, visfatin and adiponectin [9,10]. Visfatin is a pre-B cell colony-enhancing factor that is highly expressed in human visceral fat [11]. Patients with type 2 diabetes mellitus expressed higher plasma visfatin concentrations than normoglycemic individuals [12]. Although there are indications of visfatin being related to increased cardiovascular risk in the diabetic population, the data available are extremely limited [13]. However, adiponectin is a vasoactive peptide with anti-inflammatory and antiatherosclerotic properties on endothelial cells, limiting the initiation and progression of vascular lesions [14]. Recently, adiponectin was associated with glomerular capillary stress in type 2 diabetes, hence promoting shedding of adiponectin and its subsequent appearance in urine. Recent studies have linked adiponectinuria to diabetic microangiopathy [7], especially nephropathy; yet, only a few studies have explored the possible link with atherosclerotic disease.

### Aim of work

The aim of this study was to evaluate serum visfatin, serum, and urinary adiponectin as early, sensitive surrogate markers of vascular atherosclerosis. We also correlated the levels of these markers to the degree of CIMT (reflecting the atherosclerotic burden) in type 2 diabetic patients.

## Patients and methods

This is a cross-sectional observational comparative study carried out in the Diabetes, Endocrinology and Metabolism center in the Faculty of Medicine, Cairo University, in the period from January 2009 to March 2011. Sixty type 2 diabetic patients were divided into two equal groups according to the presence or absence of carotid atherosclerosis as follows: group I included 30 patients with carotid atherosclerosis and group II included 30 patients without carotid atherosclerosis. Quantification of atherosclerotic burden was assessed by common carotid artery intima-media thickness (IMT) through Doppler study. Carotid atherosclerosis was defined as increased IMT and the presence of at least one discrete plaque defined as a focal thickening at least 50% more than that of the surrounding vessel wall or a locally thickened IMT greater than 1.3 mm. There were 20 healthy volunteers matched for age and sex as the control group. We excluded those aged more than 65 years, those with a history of autoimmune disease, liver impairment, renal insufficiency (creatinine > 2 mg/dl), and those with a history of present or previous malignancy.

The degree of glycemic control and multiple cardiovascular risk factors were assessed in all groups in addition to serum visfatin and urinary adiponectin. Serum adiponectin and albumin/creatinine ratio measurements were also included in the study to broaden the comparative analysis.

**Table 1 Comparison between the demographic data among the studied groups**

| Variables | Group I ($N=30$) | Group II ($N=30$) | Controls ($N=20$) | $P$ |
|---|---|---|---|---|
| Age (years) | 53.2 ± 5 | 49 ± 5.4 | 51 ± 6 | > 0.05 |
| | A | A | A | NS |
| WHR | 0.98 ± 0.13 | 0.93 ± 0.07 | 0.85 ± 0.06 | < 0.001 |
| | A | A | B | HS |
| BMI | 31 ± 2.5 | 29.9 ± 2 | 26.3 ± 1.2 | < 0.001 |
| | A | A | B | HS |
| Duration (years) | 9.2 ± 4 | 4.3 ± 2 | – | < 0.001 |
| | A | B | – | HS |
| Sex [*n* (%)] | | | | |
| Male | 4 (13.3) | 2 (6.7) | 8 (40) | < 0.001 |
| Female | 26 (86.7) | 28 (93.3) | 12 (60) | |
| | A | A | B | HS |
| Smoking [*n* (%)] | | | | |
| No | 25 (83.3) | 29 (96.7) | 17 (85) | > 0.05 |
| Yes | 5 (16.7) | 1 (3.3) | 3 (15) | |
| | A | A | A | NS |

Groups with different letters and colors are statistically significantly different at a $P$ value of 0.05 using the Tukey post-hoc test.
HS, highly significant.

**Table 2 Laboratory results of the different groups**

| Variables | Group 1 ($N=30$) | Group 2 ($N=30$) | Controls ($N=200$ | $P$ |
|---|---|---|---|---|
| FBS (mg/dl) | 142 ± 33 | 129 ± 40 | 80.7 ± 15 | < 0.001 |
| | A | A | B | HS |
| 2HPP (mg/dl) | 211 ± 67 | 187.6 ± 62 | 124 ± 12.6 | < 0.001 |
| | A | A | B | HS |
| HBA1c% | 9.4 ± 1.3 | 7.6 ± 1.1 | 5.6 ± 0.4 | < 0.001 |
| | A | B | C | HS |
| Creatinine (mg/dl) | 0.78 ± 0.2 | 0.75 ± 0.2 | 0.60 ± 0.2 | < 0.05 |
| | A | A | B | S |
| Urea (mg/dl) | 25.4 ± 6 | 27 ± 8.1 | 23 ± 6.7 | > 0.05 |
| | A | A | A | NS |
| HDL (mg/dl) | 41.2 ± 6 | 50 ± 9.3 | 59 ± 4.1 | < 0.001 |
| | A | B | C | HS |
| LDL (mg/dl) | 148 ± 27 | 127 ± 28 | 108 ± 17 | < 0.001 |
| | A | B | C | HS |
| TG (mg/dl) | 164 ± 67 | 159 ± 63 | 102.5 ± 25 | < 0.001 |
| | A | A | B | HS |

Groups with different letters and colors are statistically significantly different at a $P$ value of 0.05.
FBS, fetal bovine serum; HDL, high-density lipoprotein; LDL, high-density lipoprotein; TG, triglyceride.

### Statistical analysis

Analysis of data was carried out by an IBM (USA) computer using statistical program for social science (version 12). $P$ value was considered significant when less than 0.05.

## Results

Tables 1 and 2 show the demographic and laboratory data of the studied groups. Table 2 shows the statistically significant difference between the studied groups in laboratory results using the one-way analysis of variance test.

Table 3 shows that group I had a higher level of serum visfatin compared with group II. Both diabetic groups had higher levels of visfatin than the controls. Furthermore, urinary adiponectin and serum adiponectin were

**Table 3 Comparison of visfatin, urinary, and serum adiponectin**

| Variables | Group 1 ($N=30$) | Group 2 ($N=30$) | Controls ($N=20$) | $P$ |
|---|---|---|---|---|
| Urinary adiponectin (μg/g) | 8.9 ± 3 | 6.6 ± 3 | 3.7 ± 1.9 | <0.001 |
| | A | A | B | HS |
| Serum adiponectin (μg/ml) | 7 ± 3.3 | 6.2 ± 1.9 | 10.6 ± 2.5 | <0.001 |
| | A | A | B | HS |
| Visfatin (ng/ml) | 45.6 ± 8 | 27.6 ± 5 | 22.1 ± 7 | <0.001 |
| | A | B | C | HS |
| ACR (mg/ml) | 123 ± 57 | 80.5 ± 38 | 14.9 ± 4 | <0.001 |
| | A | B | C | HS |

Groups with different letters and colors are statistically significantly different at a $P$ value of 0.05.
ACR, albumin/creatinine ratio.

**Table 4 Correlation between variables and carotid intimal thickness carotid intima-media thickness among diabetic patients**

| | CIMT | Visfatin | Serum adiponectin | Urinary adiponectin | ACR |
|---|---|---|---|---|---|
| CIMT | | | | | |
| *R* | – | **0.798** | 0.149 | **0.321** | **0.467** |
| *P* | – | <**0.001** | 0.255 | **0.012** | <**0.001** |
| Visfatin | | | | | |
| *R* | **0.798** | – | 0.063 | 0.223 | **0.424** |
| *P* | <**0.001** | – | 0.630 | 0.087 | **0.001** |
| Serum adiponectin | | | | | |
| *R* | 0.149 | 0.063 | – | **0.329** | 0.028 |
| *P* | 0.255 | 0.630 | – | **0.010** | 0.830 |
| Urinary adiponectin | | | | | |
| *R* | **0.321** | 0.223 | **0.329** | – | **0.462** |
| *P* | **0.012** | 0.087 | **0.010** | – | <**0.001** |
| ACR | | | | | |
| *R* | **0.467** | **0.424** | 0.028 | **0.462** | – |
| *P* | <**0.001** | **0.001** | 0.830 | <**0.001** | – |

Bold values signifies statistical values.
ACR, albumin/creatinine ratio; CIMT, carotid intima-media thickness.

significantly higher among the controls. However, group I had higher albumin/creatinine ratio (ACR) and visfatin compared with group II.

We found a statistically significant positive correlation between urinary adiponectin and diabetes duration, HBA1c, and serum creatinine. Serum visfatin correlated positively to the duration of illness, systolic blood pressure, diastolic blood pressure, and CIMT in group I patients using a correlation coefficient test.

Group I had higher levels of CIMT ($1.66 \pm 0.2$) compared with group II ($0.79 \pm 0.2$). The latter group had higher levels than the control group ($0.57 \pm 0.04$). The difference was highly significant among the different groups ($P<0.001$).

In Table 4, we used standard multiple regression to assess the predictive ability of visfatin, urinary adiponectin, serum adiponectin, and ACR to CIMT in diabetic patients. It also shows the correlation between the different variables. The model is significant ($F=28.1$, $P<0.001$).

We constructed four regression models as shown in Table 5 to assess the predictive ability of visfatin to CIMT after adjusting for urinary adiponectin, serum adiponectin, and ACR. Model 1, with all of the four factors, had $R^2$ equal to 0.647, thus explaining 65% of the variability in CIMT, with visfatin being the only significant predictor in the model ($\beta=0.03$, $P<0.001$).

Model 4 with visfatin alone still proved significant (Table 5) ($F=101.7$, $P<0.001$), explaining 63% of the variability in CIMT ($\beta=0.03$, $P<0.001$). Further adjustments made for age, sex, SMI, systolic and diastolic blood pressures, lipid profile, and blood glucose levels did not alter the results.

## Discussion

Diabetes mellitus is known to lead to a higher predisposition to atherosclerotic disease [2]. We found significantly higher serum visfatin in both diabetic groups in comparison with the control participants (Table 3). Visfatin was also significantly higher in diabetics with carotid atherosclerosis than in those without carotid atherosclerosis. Moreover, in diabetics with carotid atherosclerosis, we found a highly significant positive correlation between serum visfatin on the one hand, and the degree of CIMT, systolic, and diastolic blood pressure, as well as duration and degree of glycemic control on the other.

Visfatin, an adipocytokine produced by macrophages in visceral fat, is identical to pre-B cell colony-enhancing factor secreted by the lymphocytes. Evidence exists that visfatin exerts autocrine and endocrine effects in the liver, muscle, and heart cells, where it is also produced [11]. Studies have shown a strong correlation between visfatin and increased visceral obesity (as shown by CT scan) and a weaker one with subcutaneous fat [15].

In fact, some recent studies [16,17] found a positive correlation of visfatin with BMI and WHR, implicating its association with obesity and showing a potential link between diabetes-related insulin resistance and obesity. However, other studies presented contradictory results [9,18]. This may be partly because of the considerable differences found in visfatin immunoassays [9].

In agreement with our results, Lopez Bermejo *et al.* [19] found that visfatin levels were partly associated with higher glycated hemoglobin levels (A1C), suggesting a possible link between higher visfatin levels and progressive β-cell dysfunction. Nevertheless, Takebayashi *et al.* [20] found no correlation between diabetes and visfatin, whereas another study reported decreased visfatin in patients with type 1 diabetes mellitus and an inverse relationship between A1C and visfatin levels [21].

Visfatin has also been reported to correlate with ultrasound-evident carotid atherosclerosis in patients with metabolic syndrome [22]. Lu *et al.* [23] found higher visfatin levels in Chinese individuals with stroke, suggesting a possible role of visfatin in the development and progression of cerebrovascular disease. Diabetes

**Table 5 Regression model to assess the predictive capacity of the different variables to carotid intima-media thickness**

| | | Unstandardized coefficients | | | |
|---|---|---|---|---|---|
| Model | Predictors | $\beta$ | SE | *P* value | $R^2$ |
| 1 | Constant | −0.145 | 0.151 | 0.341 | **0.647** |
| | Serum adiponectin | 0.013 | 0.015 | 0.377 | |
| | Urinary adiponectin | 0.009 | 0.010 | 0.400 | |
| | ACR | 0.001 | 0.001 | 0.207 | |
| | Visfatin | **0.030** | **0.004** | <**0.001** | |
| 2 | Constant | −0.140 | 0.150 | 0.355 | **0.649** |
| | ACR | 0.001 | 0.001 | 0.071 | |
| | Serum adiponectin | 0.017 | 0.014 | 0.207 | |
| | Visfatin | **0.030** | **0.004** | <**0.001** | |
| 3 | Constant | −0.035 | 0.127 | 0.781 | **0.645** |
| | ACR | 0.001 | 0.001 | 0.072 | |
| | Visfatin | **0.031** | **0.004** | <**0.001** | |
| 4 | Constant | 0.008 | 0.127 | 0.951 | **0.631** |
| | Visfatin | **0.033** | **0.003** | <**0.001** | |

Bold values signifies statistical values.
ACR, albumin/creatinine ratio.

mellitus, being itself a state of chronic low-grade inflammation, together with the inflammatory state in carotid atherosclerotic plaques, increases the macrophage population, which in turn could increase the production of visfatin. This may result in a vicious positive cycle of inflammation. However, the exact association between visfatin and carotid atherosclerosis warrants further larger scale prospective studies. Nevertheless, this can partly explain the link between obesity, insulin resistance, β-cell dysfunction, endothelial dysfunction, and atherosclerosis [15].

Our study proved a significant positive correlation between serum visfatin and ACR in diabetic patients. Yilmaz *et al*. [7] also showed that visfatin levels were associated positively not only with insulin resistance but also with the degree of albuminuria in type 2 diabetic patients. Thus, endothelial dysfunction in early diabetic nephropathy is associated with altered circulating levels of visfatin.

Visfatin is synthesized in cultured mesangial cells [4]. Visfatin also stimulates glucose uptake in glomerular mesangial cells [4,7]. Thus, it was hypothesized that visfatin may contribute toward acceleration of diabetic nephropathy through aggravation of metabolic alterations [4,12]. Whether visfatin could be considered as a surrogate marker of diabetic nephropathy and whether its modulation could play a role in possible therapeutic strategies warrants further studies.

Our study found higher urinary adiponectin levels in diabetics compared with the control group and higher levels in diabetics with carotid atherosclerosis versus those without carotid atherosclerosis. In addition, we found a moderately significant positive correlation between urinary adiponectin level and the degree of CIMT as well as ACR. Von Eynatten *et al.* [24] reported findings that were in agreement with ours. They found that urinary adiponectin was significantly increased in type 2 diabetes and that adiponectinuria was associated with increased IMT. Moreover, we found that urinary adiponectin was correlated positively with the duration of diabetes and degree of glycemic control evidenced by the level of HbA1c among diabetics with carotid atherosclerosis, which was not established in the previous studies.

Previous studies addressing microalbuminuria alone and the association with CIMT showed conflicting results [2,25,26]. Microalbuminuria has been used as a marker of endothelial dysfunction and predicts CVD in patients with type 2 diabetes [1,2]. However, risk prediction by assessment of urinary albumin levels shows some important limitations. A diabetes duration of more than 6 years may precede the first appearance of urinary albumin [2,27], and vascular changes start long before the first appearance of albumin in urine and even before the diagnosis of diabetes [27]. Hence, it appears that the applicability of microalbuminuria for CVD risk evaluation in type 2 diabetes *per se* is limited. Moreover, in large prospective cohort studies, the increased risk for CVD started from urinary albumin levels well below the cutoff for microalbuminuria [24]. Thus, a considerable percentage of high-risk patients will be missed by screening for albuminuria utilizing current cut-off values. This has been supported recently by data in the Finnish Diabetic Nephropathy (FinnDiane) Study, in which a significant number of type 1 diabetic patients at high risk of premature death had normoalbuminuria [28]. Hence, newer, more sensitive detectors of early diabetic atherosclerosis are warranted.

In agreement with our study, von Eynatten *et al.* [24] showed that serum adiponectin was significantly lower in diabetics in comparison with the control group and lower in diabetics with carotid atherosclerosis than in those without carotid atherosclerosis. However, in contrast to von Eynatten *et al*. [24], we failed to establish a significant positive correlation of serum adiponectin levels with the degree of CIMT. It was shown in type 2 diabetic patients that adiponectin is the lowest in the presence of impaired glucose regulation and early diabetes, whereas long diabetes duration is associated with a significant increase in circulating adiponectin levels [4]. Hence, hypoadiponectinemia may have clinical value at the early stages of atherogenesis, but at more advanced disease stages, its role as a meaningful biomarker is questionable [14].

Although previous studies have evaluated markers such as serum visfatin [28,29], urinary adiponectin [4], ACR, and serum adiponectin [14] as novel markers of vascular damage in diabetes, this is the first comparative study including all four variables to assess their predictive value, sensitivity, and specificity in the degree of increase in IMT (reflecting macrovascular disease in type 2 diabetes and CVD risk evaluation) both collectively and separately.

Our study established that serum visfatin exceeded urinary and serum adiponectin as well as ACR as a highly valid marker of increased CIMT with 100% sensitivity and 92% specificity. Furthermore, serum visfatin was the only significant predictor in our stepwise regression model (including all four variables), explaining 65% of the variability in CIMT. This was still significant after controlling for urinary adiponectin, serum adiponectin, and ACR. In fact, visfatin alone accounted for 63% of the variability in CIMT. Urinary adiponectin exceeded ACR in sensitivity (83 and 80%, respectively) whereas ACR had a higher specificity (65 and 60%, respectively) for increased CIMT.

Ultrasonic measurement of CIMT has been used for several years as a surrogate for predicting rates of cardiovascular events. However, this is limited by the fact that age-related thickening IMT of the CCA also occurs in the absence of overt atherosclerosis. This has been shown in some human and animal models [2,27], which is not synonymous with atherosclerosis. In addition, regression of IMT has been found to be poorly predictive of reduction in cardiovascular events in a meta-analysis of published studies [2].

The relatively small sample size and cross-sectional design of our study did not allow us to infer a causal relationship of visfatin and urinary adiponectin with subclinical atherosclerosis and subsequent CVD events.

Nevertheless, the significant correlation between serum visfatin with the degree of IMT indicates that visfatin levels may play a role as an earlier and cheaper detector of atherosclerotic changes in the subclinical phase. Hence, early detection of atherosclerotic changes through elevated visfatin levels may possibly over-ride the need for atherosclerotic burden assessment by radiological methods. This provides for early prediction and management of transient ischemic attacks and vertebrobasilar insufficiency.

## Conclusion

Serum visfatin may emerge as a valuable and cheaper surrogate marker for prevalent macrovascular complications in a type 2 diabetic population. It is a novel and easy-to-use method for the clinical assessment of vascular stress and CVD risk in type 2 diabetes. Future prospective studies are needed to confirm our results.

## Acknowledgements

### Conflicts of interest

There are no conflicts of interest.

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