New Biomarkers as Prognostic Factors for Cardiovascular Complications in Type 2 Diabetic Patients

Hanaa H. Ahmed¹ · Wafaa Gh. Shousha² · Hatem A. El-mezayen² · Ibrahim A. Emara³ · Marwa E. Hassan³

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Abstract This study was initiated to explore some novel biomarkers like pro-inflammatory markers (chemerin and visfatin) and anti-inflammatory marker (omentin-1) as prognostic factors for cardiovascular complications in type 2 diabetic patients. Forty diabetic patients without cardiovascular disease, 40 diabetic patients with cardiovascular disease and twenty healthy control counterparts were included in this study. Serum chemerin, omentin-1 and visfatin levels were quantified. Receiver operating characteristic curve analysis was done to identify the cut off value for each marker. The mean serum level of chemerin was 57.65 ± 15.69 ng/l in diabetic patients versus 93.97 ± 26.62 ng/l for the cardio-diabetic ones ($P < 0.0001$). The mean serum level of omentin-1 was 8.77 ± 1.53 ng/ml in diabetic patients versus 1.76 ± 0.96 ng/ml for the cardio-diabetic ones ($P < 0.0001$). The mean level of visfatin was 1.44 ± 0.71 ug/l in diabetic patients versus 3.92 ± 3.32 ug/l for the cardio-diabetic ones ($P < 0.0001$). Chemerin and Visfatin levels were significantly enhanced in the cardio-diabetic patients with increasing C-reactive protein (CRP), triglycerides (TG), fasting blood glucose (FBG), micro-albumin and cholesterol. Omentin-1 level was significantly reduced in the cardio-diabetic patients with increasing CRP, TG, FBG, and cholesterol. It was observed that the area under

curve for chemerin, omentin-1 and visfatin was 0.877, 0.998 and 0.735, respectively. In conclusion, this study evidences that the measuring serum levels of chemerin, omentin-1 and visfatin may help in the prognosis of cardiovascular complications in type 2 diabetic patients.

Keywords Diabetes mellitus · Cardiovascular complications · Chemerin · Omentin-1 · Visfatin · Prognosis

Introduction

Diabetes mellitus is a chronic disease that affects 415 million people worldwide and 5 million people died from diabetes-related complications [1]. Type 2 diabetes mellitus (T2DM) is manifested by hyperglycemia, that results from lack of endogenous insulin or resistance to the action of insulin in fat, muscle, and liver in addition to an insufficient response by beta cells of pancreas [2].

T2DM is a major risk factor for cardiovascular disease (CVD). This is due to a complex group of common factors associated with T2DM including hypertension, insulin resistance, hyperglycemia, hyperinsulinemia, diabetic dyslipidemia, systemic inflammation and fat tissue-derived factors [3].

Fat tissue is now considered as an active endocrine organ and secretes biologically active molecules (adipokines) that signal to the brain, liver, skeletal muscle, and the immune system, the important metabolic organs in the body [4, 5]. These adipokines include chemerin, omentin-1 and visfatin [5, 6].

Chemerin is a pro-inflammatory cytokine that potentiates immune cells and implicates in inflammation by activating macrophage adhesion to vascular cell adhesion molecule-

✉ Hanaa H. Ahmed
hanaaomr@yahoo.com

¹ Hormones Department, National Research Centre, Dokki, Giza, Egypt

² Biochemistry Department, Faculty of Science, Helwan University, Cairo, Egypt

³ Biochemistry Department, National Institute of Diabetes and Endocrinology, Cairo, Egypt

1(VCAM-1) and fibronectin [7]. It is not only a marker of vascular damage [8] but also a prognostic predictor [9]. In addition, chemerin is associated with glucose and lipid metabolism, inflammation, and adipogenesis. All of these lead to the development for cardio-vascular complications in diabetic patients, especially atherosclerosis [10].

Omentin-1, a recently identified as fat deposition-specific adipokine codified by two genes (1 and 2), is highly expressed in visceral omental adipose tissue [6]. Omentin-1 level showed negative correlation with fasting insulin, waist circumference, body mass index (BMI), and homeostasis mFadodel assessment (HOMA) index. Meanwhile, it revealed positive correlation with high density lipoprotein cholesterol (HDL-C) [11]. In addition, Yamawaki et al. [12] demonstrated a vasodilating effect of omentin-1 on isolated blood vessels, suggesting omentin-1 involvement in endothelial function. Thus omentin-1 might be contributed in CVD due to a possible association with inflammation and endothelial function.

Visfatin is a new adipokine that is synthesized in visceral adipose tissue; both its expression and plasma level increase in humans with type 2 diabetes mellitus or abdominal obesity [13]. Visfatin binds to insulin receptor at a site different from that of insulin exerting hypoglycemic action by inhibiting the release of glucose from hepatic cells and activating glucose uptake in peripheral tissues [14]. Also, visfatin is recognized in inflammatory cells and its concentration is increased in several inflammatory diseases and metabolic disorders, including cardiovascular complications [14, 15].

The focus of our interest was to assess some new biomarkers as prognostic factors for cardiovascular complication in type2 diabetic patients. These included as anti-inflammatory marker (omentin-1) and pro-inflammatory markers (chemerin, and visfatin).

Subjects and Methods

Forty diabetic patients with cardiovascular disease (cardio-diabetic group) and 40 diabetic patients without evidence of CVD (diabetic group) were participated in the current study. In addition, twenty healthy subjects who with no history of T2DM, other endocrine dysfunctions, hyperlipidemia, hypertension, or coronary heart diseases were enrolled in the study and served as controls. Clinical evidence of CVD included myocardial infarction or coronary artery by-pass surgery, stroke, and peripheral arterial disease. Patients in the group without vascular disease were T2DM patients who had no history of vascular disease and those with normal ECG findings at exercise and normal peripheral artery doppler ultrasonography findings. Exclusion criteria involved the presence of sustained type 1 DM, acute and chronic infections, malignancy, hepatic or renal

disease, diabetic retinopathy and nephropathy, and other endocrine dysfunctions. This study was approved by Ethical Committee of Ethics commission and Scientific Research of the General Authority for Hospitals and Educational Institutes.

Venous blood samples and urine samples were collected from all participants and each blood sample was divided into two portions. The small portion was collected on EDTA coated tube and the large portion was collected on EDTA free coated tube. Serum samples were obtained by centrifugation and the biochemical variables were measured on the same day of the blood collection. Remaining serum specimens were stored at -20°C until analysis of omentin-1, chemerin, and visfatin levels.

Quantitative determination of Serum glucose, cholesterol, HDL-cholesterol and triglycerides levels were carried out colorimetrically using commercial kit purchased from Randox Laboratories. Serum LDL-cholesterol and glycated hemoglobin levels quantified using kit provided by Spinreact. Serum chemerin, omentin and visfatin concentrations were evaluated by solid-phase enzyme-linked immunosorbent assay (ELISA kit) using 96-well microplates supplied by Glory Science Co., Ltd. Serum C-reactive protein (CRP) was measured by ELISA using commercial kit purchased from Immunospec Corporation. Quantitative estimation of micro-albumin in urine was done by immunoturbidimetric assay using commercial kit purchased from Pointe Scientific, INC.

Statistical Analysis

Data were expressed as mean $\pm$ standard deviation (SD) and analyzed using MedCalc software, version 11. The Student's t test was used to assess the significance of difference in the levels of chemerin, omentin-1 and visfatin between the patient groups (diabetic and cardio-diabetic) and the control group. The correlation analysis between serum chemerin, omentin-1, and visfatin level and other measured parameters in the cardio-diabetic group was performed by correlation coefficient test. The cut-off value was determined for each of the studied parameters in the current study according to the best discrimination between diabetic patients and cardio-diabetic patients regarding optimal values of sensitivity and specificity using ROC curves analysis. AUC of the ROC curve was calculated for each test. $P < 0.05$ was accepted as significant.

Results

Laboratory assessments of the measured parameters in the different submitted groups are presented in Table 1. Serum chemerin levels showed significant elevation in diabetic

Table 1 Laboratory assessments in the different studied groups

Parameters	Healthy control subject (C)	Diabetic patients (D)	Cardio-diabetic patients (CD)	P1	P2	P3
Chemerin (ng/l)	28.80 ± 6.82 20.00–40.00	57.65 ± 15.69 32.00–95.00	93.97 ± 26.62 43.00–150.0	< 0.0001	< 0.0001	< 0.0001
Omentin-1 (ng/ml)	14.73 ± 2.16 12.10–18.30	8.77 ± 1.53 6.60–12.5	1.76 ± 0.96 0.85–5.20	< 0.0001	< 0.0001	< 0.0001
Visfatin (ug/l)	1.17 ± 0.20 0.99–1.90	1.44 ± 0.71 0.98–4.20	3.92 ± 3.32 0.98–11.00	0.097	0.0005	< 0.0001

P1 Diabetic group compared to the healthy control group

P2 Cardio-diabetic group compared to the healthy control group

P3 Cardio-diabetic group compared to the diabetic group

patients versus the healthy control subjects ($P < 0.0001$). Likewise, serum chemerin and visfatin levels revealed significant enhancement in cardio-diabetic patients versus the healthy control subjects ($P < 0.0001$ and $P = 0.0005$ respectively). In addition, serum chemerin and visfatin levels exhibited significant amplification in cardio-diabetic patients relative to the diabetic patients ($P < 0.0001$ and $P < 0.0001$ respectively). Serum omentin-1 levels showed significant drop in cardio-diabetic group compared with the diabetic patients and the healthy control subjects ($P < 0.0001$). Also, omentin levels are significantly suppressed in diabetic patients versus the healthy control subjects ($P < 0.0001$).

Correlation between serum chemerin levels and metabolic parameters in the cardio-diabetic patients was depicted in Fig. 1. Significant positive correlation between serum chemerin levels and cholesterol, TG, CRP, FBG, HbA1c and visfatin levels has been recorded in the cardio-diabetic patients ($P = 0.0001$, $P < 0.0001$, $P < 0.0001$, $P = 0.005$, $P = 0.040$, and $P = 0.001$ respectively). Also, a significant positive correlation has been observed between chemerin levels and micro-albumin levels in the cardio-diabetic patients ($P = 0.011$). In addition, a significant negative correlation has been found between chemerin levels and omentin-1 levels in the cardio-diabetic patients ($P = 0.0001$).

Figure 2 illustrated the correlation between serum omentin-1 levels and metabolic parameters in the cardio-diabetic patients. A significant negative correlation between serum omentin-1 levels and cholesterol, TG, CRP, FBG, chemerin, and visfatin levels in the cardio-diabetic patients ($P = 0.054$, $P = 0.030$, $P = 0.003$, $P = 0.006$, $P = 0.0001$, $P = 0.036$ respectively) has been registered.

Correlation between serum visfatin levels and other metabolic parameters in the cardio-diabetic patients is presented in Fig. 3. The results indicated a significant positive correlation between serum visfatin levels and cholesterol, TG, CRP, chemerin, FBG and microalbumin

levels in the cardio-diabetic patients ($P = 0.005$, $P = 0.0003$, $P = 0.0001$, $P = 0.001$, $P = 0.003$ and $P = 0.018$ respectively). Meanwhile, a significant negative correlation has been found between serum visfatin levels and omentin-1 levels in the cardio-diabetic patients ($P = 0.036$).

The receiving operating characteristic (ROC) curve was designed for chemerin, omentin-1 and visfatin (Fig. 4a–c). The cut-off values for serum chemerin, omentin-1 and visfatin were 75 ng/l, 6.2 ng/ml, and 1.5 ug/l respectively. Area under curve (AUC) for chemerin, omentin-1 and visfatin was 0.877, 0.998, and 0.735 respectively. These findings indicate the good validity of the above biochemical markers particularly omentin-1 to discriminate diabetic patients from cardio-diabetic patients.

Discussion

The objective of this work is to assess some novel biomarkers as prognostic factors including anti-inflammatory markers (omentin-1) and pro-inflammatory markers (chemerin, and visfatin) for cardiovascular complications in type2 diabetic patients.

The results obtained in this study indicated that serum chemerin showed significant elevation in the diabetic patients in respect to the healthy control subjects. These findings are in agreement with the studies of El-Mesallamy et al. [16] who mentioned that chemerin levels reveal significant increase in the diabetic patients when compared to the healthy subjects. Sell et al. [17] explained these results by the fact that adipose tissue expresses chemerin and chemokine-like receptor-1, and the production of chemerin is correlated with the volume of adipocyte. Furthermore, the production of the high amount of chemerin is linked with insulin resistance at the level of lipogenesis by its reversible binding to the extracellular domain of insulin receptor-tyrosine kinase in peripheral tissues and the

Fig. 1 Correlation between serum chemerin levels and different metabolic parameters in the cardio-diabetic group

Fig. 2 Correlation between serum omentin-1 levels and different metabolic parameters in the cardio-diabetic group

Fig. 3 Correlation between serum visfatin levels and different metabolic parameters in the cardio-diabetic group

decreasing rate of auto-phosphorylation and subsequent downstream intracellular signaling cascades. Also, chemerin suppresses the phosphorylation of glycogen synthase kinase, an enzyme necessary for synthesis and storage of glycogen, and inhibits the uptake of glucose. In addition, chemerin potentiates extracellular signal-regulated kinase (ERK). It has been demonstrated that the suppression of ERK prevents chemerin-induced insulin resistance, indicating the contribution of this pathway in chemerin action.

Omentin-1 level revealed significant reduction in diabetic patients versus the healthy control subjects. This finding comes in line with the study of Yan et al. [18] who stated that plasma omentin-1 concentrations are decreased in impaired glucose tolerant and T2DM patients relative to their matched controls. Also, Abd-Elbaky et al. [19] recorded a significant drop in serum omentin-1 levels in

type 2 diabetic patients versus control counterparts. Urbanova et al. [20] reported that omentin-1 has an insulin sensitizing effect on adipocytes in both visceral and subcutaneous adipose tissue via increasing insulin signal transduction by activation of Akt/protein kinase B (Akt/PkB). Also, it enhances the uptake of glucose, that is stimulated by insulin in adipocytes.

This study indicated that there is no difference in serum visfatin levels between diabetic patients and the healthy control subjects. This finding is in harmony with the study of Takebayashi et al. [21] who didn't find any correlation between visfatin and diabetes.

Serum chemerin level showed significant amplification in cardio-diabetic patients relative to the healthy control subjects. This result agrees with that of Ying and Dongying [22] who found an increase in serum chemerin level in

Fig. 4 **a** ROC curve for differentiation between diabetic and cardio-diabetic patients by chemerin ($P = 0.0001$), **b** ROC curve for differentiation between diabetic and cardio-diabetic patients by omentin-1 ($P = 0.0001$), **c** ROC curve for differentiation between diabetic and cardio-diabetic patients by visfatin ($P = 0.0001$)

coronary artery disease (CAD) patients. Also, Liang et al. [23] recorded an elevation in serum chemerin level in acute myocardial infarction (AMI) patients compared with that in healthy subjects. This finding was explained by Wittamer et al. [24] who mentioned that chemerin promotes the migration of macrophage and immature dendritic cell and the increased accumulation of macrophages induces the rupture of plaque and the thrombus formation in advanced atherosclerosis [23]. Also, chemerin stimulates cholesterol uptake and foam cell formation. It is well known that a macrophage-to-foam cell switch elicits the initiation and development of atherosclerosis. Therefore, chemerin may be involved in the different stages of atherosclerosis via regulating the migration of macrophage.

Serum omentin-1 level revealed significant decline in cardio-diabetic patients in comparison with the healthy control subjects. This finding is in agreement with that of Xia et al. [25] who recorded lower omentin-1 level in acute coronary syndrome patients or stable angina pectoris patients compared with the healthy subjects. Moreover, the study of Abd-Elbaky et al. [19] showed that low levels of circulating omentin-1 are associated with the prevalence of coronary artery disease. It has been reported that AMP-activated protein kinase (AMPK) and Akt protect myocytes from apoptosis and ischemic injury as the activated phosphorylation of AMPK at Thr-172 and Akt at Thr-308 in the heart has been observed in omentin- treated mice [26]. In

addition, phosphorylation of AMPK and Akt in cardiac myocytes has been detected after treatment of human with omentin-1 protein as omentin-1 time-dependently enhances the phosphorylation of acetyl-CoA carboxylase, a downstream target of AMPK in cardiac myocytes. Omentin-1 also promotes Akt phosphorylation in a time dependent manner. Therefore, these data suggest that omentin-1 protects the heart from ischemic injury.

From another point of view, Yoshiyuki et al. [26] proved that omentin-1 enhances the phosphorylation of endothelial nitric oxide synthase in both ischemic muscles and cultured endothelial cells and promotes vasodilation of isolated aorta. In addition, omentin-1 reduces tumor necrosis factor- α -activated expression of adhesion molecules in endothelial cells via suppression of NF- κ B pathway. Collectively, omentin-1 can modulate endothelial function and inflammatory response in the heart in addition to its pro-survival properties, thereby contributing to protection against myocardial ischemic injury.

Serum visfatin level showed significant elevation in cardio-diabetic patients versus the healthy control subjects. Similar results have been recorded by Zakaria et al. [27] who found that serum visfatin level is higher in diabetics with microvascular complications than in non complicated diabetics and controls. Tania et al. [28] mentioned that the increased circulating visfatin/Nampt levels correlates with the development of atherosclerotic plaques. These investigators demonstrated that visfatin/Nampt can directly potentiate vascular inflammation by stimulating different cell types such as endothelial cells and vascular smooth muscle cells. Exogenous administration of visfatin/Nampt activates ERK 1/2 and NF- κ B, resulting in enhanced expression of the inducible nitric oxide synthase (iNOS) [29] which is a pro-inflammatory enzyme playing a critical role in endothelial dysfunction and vascular injury in diabetes-related vascular complications [30].

Serum chemerin level revealed significant increase in cardio-diabetic patients with respect to diabetic patients. Chemerin was proved to be a functional protein in human inflammatory fluids that served as the ligand of chemR23 [24]. Both chemerin and chemR23 are expressed at highest levels in white adipose tissue, playing a critical role in adipogenesis and adipocyte metabolism. In this way, chemerin may be contributed in the development of cardiovascular complications, especially atherosclerosis in diabetic patients [31].

The current study revealed significant positive correlation between serum chemerin levels and cholesterol, TG, CRP, FBG, HbA1C, and visfatin cardio-diabetic patients. Likewise, significant positive correlation has been detected between serum chemerin level and LDL in diabetic patients. These results echo those of Ying and Dongying [22] who registered significant positive association

between serum chemerin and triglycerides, and hs CRP in CAD patients.

In the present work, significant negative correlation has been found between serum chemerin and omentin-1 levels in the cardio-diabetic patients. These results are in agreement with those of El-Mesallamy et al. [16.] who observed a significant negative correlation between levels of omentin-1 and chemerin in diabetic patients with or without ischemic heart disease. The present results revealed also significant positive association between micro-albumin and chemerin levels in the cardio-diabetic subjects.

In the present investigation the level of omentin-1 was significantly lower in cardio-diabetic patients than in diabetic patients. Dysregulation of secretion of omentin-1 plays an important role in the pathophysiology of endothelial dysfunction, insulin resistance, inflammation and cardiovascular disease [32].

Significant negative correlation between serum omentin-1 level and cholesterol, TG, CRP, FBG, chemerin and visfatin in cardio-diabetic group has been registered in the present study. These results are in agreement with those of Shibata et al. [33] who noted that plasma level of omentin-1 correlates negatively with the level of cholesterol in acute coronary syndrome patients or stable angina pectoris patients. In addition, Abd-Elbaky et al. [19] found that omentin-1 level is negatively correlated with cholesterol levels in diabetic patients with cardiovascular disease.

The serum visfatin level was significantly higher in cardio-diabetic patients when compared to diabetic one. Positive associations between enhanced circulating visfatin/nampt levels and atherogenic inflammatory diseases have been established supporting a role of visfatin as a potential biomarker for cardiovascular complications associated with metabolic disorders [27, 28].

Also, the present results revealed significant positive correlation between visfatin and cholesterol, TG, CRP, FBG and micro-albumin in cardio-diabetic patients. Visfatin can activate the adhesion of leukocytes to aortic endothelium by activating intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1. This phenomenon appears to be mediated through the pro-inflammatory transcription factor (nuclear factor-KB9) in a reactive oxygen species (ROS) dependent manner.

ROC curves were done to detect the best cut off values of serum chemerin, omentin-1 and visfatin in diabetic and cardio-diabetic patients. It has been found that chemerin at concentration 75 ng/l has 80% sensitivity and 90% specificity. These findings suggest that chemerin is a biomarker of CVD in patients with type 2 diabetes mellitus. Omentin-1 at concentration 6.2 ng/ml has 97% sensitivity and 100% specificity. These data propose that omentin-1 may represent a biomarker for not only metabolic disorders, but also CVD. Visfatin in diabetic and cardio-diabetic patients at

concentration 1.5 µg/l has 67.5% sensitivity and 77.5% specificity. These findings postulate that visfatin is a biomarker of CVD in patients with type 2 diabetes mellitus.

In conclusion this study evidences the usefulness of measuring chemerin, omentin-1 and visfatin as prognostic tools for cardiovascular complications in patients with type 2 diabetes mellitus. Omentin-1 in particular represents the best predictor marker for cardiovascular complications in these patients.

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