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Plasma Adiponectin and Resistin Levels in Type 2 Diabetic Obese Female Patients With and Without Hypertension and Retinopathy

Seham M. S. EL – Nakeeb*, Manal A.Lattif, Ahmed M.Ragheb***, Adel Balaha***, Baker M.A. Albow******

Biochemistry Dept.* Internal Medicine Dept.** Faculty of Medicine for Girls AL-Azhar University Clinical Pathology Dept.*** Faculty of Medicine AL-Azhar University, Faculty of Medical Technology****,Mesalata- El- Margeb University.

Abstract

Background: In the past, adipose tissue was largely regarded as a depot for fuel storage in the form of triglyceride. However, adipose tissue is an active endocrine organ that secretes a variety of metabolically important substances including adipokines. The adipocyte is now known to secrete a variety of proteins such as tumour necrosis factor (TNF)-α, adipsin, plasminogen activator inhibitor-1, leptin, resistin, and adiponectin. Adipose tissue regulates insulin sensitivity via the circulating adipocytokines, resistin and adiponectin. These factors affect insulin sensitivity and may represent a link between obesity, insulin resistance and type 2 diabetes (DM). The objective of this study was to compare the levels of resistin and adiponectin in type 2 diabetic obese female patients with and without hypertension and retinopathy.

Subjects and Methods: In this study the plasma adiponectin and resistin concentrations were investigated, in 20 control obese non-diabetic females and 40 obese female patients with type 2 diabetes mellitus. The diabetic females were divided into 2 groups. G_I included 20 controlled uncomplicated diabetics & G_{II} included 20 diabetic patients with hypertension and retinopathy.

Results: The plasma concentration of adiponectin was significantly lower ($P< 0.01$) in diabetic females in G_I & G_{II} than non-diabetic control females. In diabetic patients with hypertension and retinopathy (G_{II}) there was a significant decrease in plasma adiponectin levels ($P< 0.01$) as compared to their levels in diabetic females in G_I and control females. Our results also show that there were non-significant changes in plasma resistin in diabetic patients in both groups G_I & G_{II} as compared to their levels in control group.

Conclusion: These results suggest that adiponectin may play a key role in pathophysiology of type 2 diabetes mellitus and its microangiopathy and macrovascular complications.

Key words: diabetes mellitus **.** obesity . adiponectin . resistin.

Introduction

Obesity is associated with an increased incidence of diabetes, hypertension, dyslipidaemia and coronary artery disease. Current management strategies of obesity include lifestyle interventions and pharmaco therapy (Filippatos *et al.*, 2005) .Overweight (BMI $\geq$ 25 kg/m^2) and obesity (BMI $\geq$ 30 kg/m^2) are becoming increasingly prevalent in the industrialized world (James *et al.*, 2001), not only in type 2 but also in type 1 diabetic patients (Libman *et al.*, 2003 and Kibirige *et al.*, 2003). Besides physical inactivity, intensive insulin therapy to obtain good metabolic control to reduce complications is associated with weight gain (Williams *et al.*, 1999 and DCCT Research Group, 1993). The relationship between metabolic control and the development of chronic complications (retinopathy, neuropathy, and nephropathy) is a primary concern of clinicians. Factors involved in the development of vascular complications of diabetes include long diabetes duration, poor glycemic control,

smoking, hypertension, and dyslipidemia, but the role of body weight/BMI is unclear (De Block *et al.*, 2005).

Retinopathy may not only be related to glycemic control and diabetes duration but also to blood pressure and BMI for patients with type 2 diabetes, as was shown by the U.K. Prospective Diabetes Study (1998) and the Hoorn Study (van Leiden *et al.*, 2002). However, information on the possible role of BMI on retinopathy in type 2 diabetes is scarce. Zhang *et al.* (2001) revisited data from the Diabetes Control and Complications Trial and observed that besides diabetes duration and metabolic control, BMI had a significant predictive value in developing retinopathy. In Sweden, Henricsson *et al*. (2003) observed that time to develop retinopathy was related to high HbA_1c (A_{1C}) and high BMI. Only one recent report suggested a role of BMI in neuropathy (Tesfaye *et al.*, 2005). Adipocytokines, products from adipose tissue, have biological activities on the vascular system and may affect diabetic microangiopathy. Despite the abundance of studies on adipocytokines among type 2 diabetic patients or healthy individuals, there is only one study dealing with adiponectin and macrovascular complications in type 1 diabetes (Costacou *et al.*, 2005). Because overweight is becoming increasingly prevalent and can be managed by lifestyle intervention (nutrition, exercise, and education), it seems appropriate to study the impact of overweight, which may reduce the impact of good metabolic control, on diabetes complications.

Adiponectin is an anti-diabetic and anti-atherogenic hormone that is exclusively secreted from fat cells. Serum adiponectin levels are reduced in obese patients and obese model mice, despite increased adipose tissue mass. Elucidation of the mechanism(s) by which plasma adiponectin levels are decreased in obese and diabetic patients would provide insight into the cause of obesity-induced diabetes and the development of therapeutic advances. In the Kamon *et al.*, study, the regulation of adiponectin secretion was investigated using 3T3-L1 adipocytes and a diabetic-/obese-mouse model. A novel insulin sensitizer, IkappaB kinase beta (IKK beta) inhibitor, ameliorated insulin resistance and up-regulated plasma levels of adiponectin without producing a significant change in body weight in KKAy mice that were fed a high-fat diet. The IKKbeta inhibitor cancelled the TNF alpha-mediated down-regulation of adiponectin secretion and simultaneously up-regulated the phosphorylation of Akt in 3T3-L1 adipocytes. Using dominant-negative mutants of Akt or PKClambda (downstream effectors of phosphoinositide 3-kinase), insulin-stimulated Akt activity was found to be important in the regulation of adiponectin secretion by insulin in 3T3-L1 adipocytes. These observations suggest that "insulin-stimulated Akt activity in adipocytes" may play an important role in the regulation of adiponectin secretion (Kamon *et al.*, 2004).Adiponectin deficiency leads to enhanced thrombus formation and platelet aggregation. The study of Kato *et al.* (2005) reveals a new role of adiponectin as an endogenous antithrombotic factor.

Resistin, an insulin inhibitor secreted by adipocytes, is associated with obesity and insulin resistance in mice. The role of resistin in human biology remains uncertain. Hasegawa *et al.*, observed that resistin levels were increased significantly in patients with type 2 diabetes compared with non-diabetic subjects. However, there was no correlation in either patient groups between serum resistin levels and markers of insulin resistance, obesity or hyperlipidaemia. These results were in direct contrast to the data of leptin or adiponectin, both of which were closely related to these clinical markers of diabetes. Multivariate regression analysis on the combined data of the two groups demonstrated that the presence of diabetes and HDL cholesterol levels were significant predictors of serum resistin levels. No correlation was observed between C-reactive protein and resistin adjusted for BMI. Taken together, these findings demonstrate that serum resistin levels are increased in patients with type 2 diabetes, but this increase is not linked to markers of insulin resistance or adiposity (Hasegawa *et*

al., 2005). Further studies are necessary to elucidate the significance of serum resistin concentration in human pathophysiology. Our study aimed to assess the plasma adiponectin and resistin levels in type 2 diabetic obese female patients with and without hypertension and retinopathy.

Subjects and Methods

Subjects

Forty obese female patients with type 2 diabetes were selected for the present study from diabetic care unit in Al-Zahraa University Hospital. Participants with renal or liver dysfunction or active infection were excluded. They were divided into 2 groups. Group I (G_I) included 20 diabetic females aged 48-59 years ,having diabetes for the past 5-10 years. All patients in G_I had no history of diabetic ketoacidosis, nephropathy, cardiovascular disease and not suffering from any complications. Group II (G_{II}) included 20 diabetic females with hypertension (blood pressure ≥130/90) and retinopathy (retinopathy was examined by fundoscopy), aged 50-62 years, having diabetes for the past 9-12 years. Nine patients had a history of diabetic ketoacidosis and eight patients had a history of coronary artery disease. All patients with diabetes were treated with metformin and had not been taking other drug medication for the last one year before entering the study. The control subjects, 20 females, aged 47 – 60 years were selected from among apparently healthy subjects. All participants gave their informed consent before the study began.

Biochemical analysis

Venous blood samples (10 ml) were collected after an overnight fasting in tubes containing EDTA and were immediately centrifuged at 1500 rpm for 15 min at 4°C. Plasma samples were protected from light & frozen at - 80°C and stored until analysis. Plasma glucose was estimated by enzymatic colorimetric glucose oxidase method (Trinder, 1969). Glycohemoglobin HbA_{1c}, was determined in whole blood by fast ion-exchange resin separation method. The HbA_{1c} % of total hemoglobin was determined by measuring the absorbance of HbA_{1c} and of the total hemoglobin fraction at 415 nm in comparison with a standard glycohemoglobin. Plasma adiponectin levels were measured using RIA kit for human adiponectin (Linco Research, Inc, St. Charles, Mo). The assay uses ^{125}I-Labeled adiponectin and an antiadiponectin rabbit antiserum to determine adiponectin concentration by double-antibody/ polyet-hylene glycol technique. Plasma resistin levels were measured using human resistin ELISA kit (BioVendor Laboratory Medicine, Inc, Brno, Czech Republic) that uses rabbit polyclonal antihuman resistin antibody.

Statistical analysis

Data was entered into IBM compatible computer then analysis were done using SPSS /PC$^+$ program for windows (Norusis, 1986). The following statistical procedures were performed (Saunders and Trapp,1990) arithmetic mean, standard deviation (± SD), ″F″ test, one way ANOVA to test for variations within groups (P– values less than 0.05 were considered significant) .

Results

Table (1) & Fig (1) show that there was a significant decrease in plasma adiponectin ($P< 0.01$) in diabetic females with and without hypertension and retinopathy,G_I & G_{II} , as compared to their levels in control group. In diabetic patients with hypertension and retinopathy (G_{II}) there was a significant decrease in plasma adiponectin levels ($P< 0.01$) and significant increase in fasting plasma glucose levels ($P< 0.05$) as compared to their levels in controlled uncomplicated diabetes patients (G_I) and control groups. Table (1) & Fig (2) also show that there were non-significant changes in plasma resistin levels in diabetic patients in all groups G_I & G_{II} as compared to their levels in control group.

Table (1) :Clinical data and hormonal characteristics of Control & diabetic patients with and without hypertension and retinopathy (G_I & G_{II})

Parameters	Control group	Controlled uncomplicated diabetes (G_I)	diabetes with hypertension and retinopathy (G_{II})	P <
Age (years)	51.4 ± 7.3	53.2 ± 10	52.4 ± 9	N.S
Weight (kg)	85.9 ± 12.7	85.6 ±14.7	87.4 ±11.6	N.S
BMI (kg/m2)	30.7 ± 7.5	31.2 ± 5.92	32.9 ± 6.73	N.S
Systemic Blood pressure **Systolic (mm Hg)** **Diastolic (mm Hg)**	 110.9 ±7.4 65.1 ±5.7	 111.2 ±12.1 67.4 ± 8.1	 176 ±16.7* 155.7 ±9.8*	 0.01 0.01
The known duration of diabetes (years)	---	7.8 ± 2.01	9.4 ± 2.37	----
Fasting plasma glucose (mM)	4.37 ± 1.5	5.24 ± 1.8	6.3 ±1.2 *	0.05
Hb A_{1c}	5.4 ± 0.1 %	5.8 ± 0.3 %	8.5 ± 0.7 %	----
Plasma adiponectin (µg/ml)	8.3 ± 3.2	6.2 ± 2.2*	4.09 ± 2.31*	0.01
Plasma resistin (ng/ml)	7.3 9± 3.9	7.95 ±2.9	8.1 ± 3.4	N.S

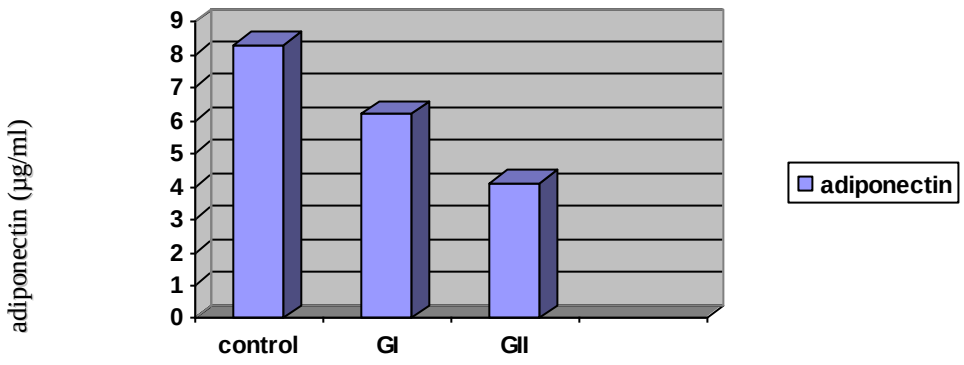
Data are expressed as the mean ± SD N.S = non-significant

* = Significant (P < 0.05)

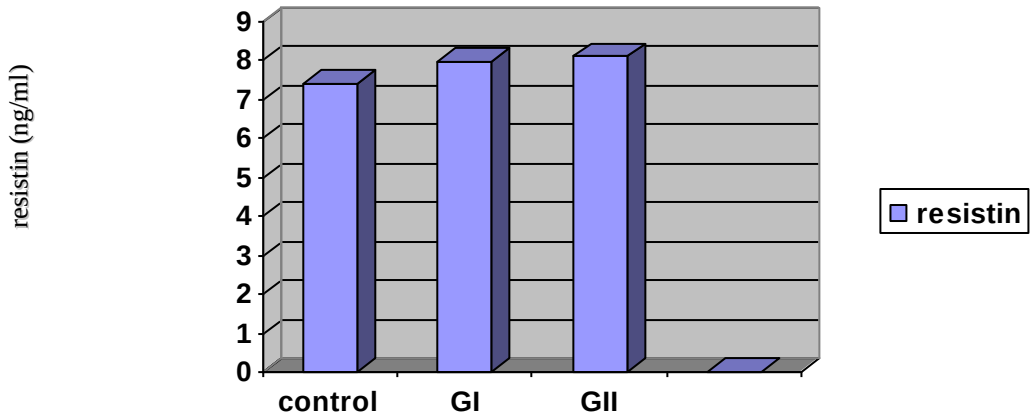
Systolic ,diastolic blood pressure ,plasma adiponectin & fasting plasma glucose in diabetes with hypertension and retinopathy (G_{II}) versus control &G_I

Plasma adiponectin in controlled uncomplicated diabetes (G_I) versus control & $G_{II.}$

Fig(1) Plasma adiponectin levels in control, G_I&G_{II}



Fig(2) Plasma resistin levels in control, G_I&G_{II}



G_I=Controlled uncomplicated diabetes
G_{II}=diabetes with hypertension and retinopathy.

Discussion

The raising prevalence of type-2 diabetes mellitus and obesity has been recognized as a major problem for public health, affecting both developed and developing countries. Impaired fasting plasma glucose has been previously associated with endothelial dysfunction, higher levels of inflammatory markers and increased risk of developing insulin resistance and cardiovascular events. Besides lifestyle changes, the blockade of the reninangiotensin system has been proposed as a useful alternative intervention to improve insulin resistance and decrease the number of new type-2 diabetes cases (Lopez-Jaramillo *et al.*, 2006).

Adiponectin and resistin are hormones that may represent a link between obesity and insulin resistance. Adiponectin, an adipocyte-derived factor, possesses anti-atherogenic properties and is decreased in patients with insulin resistance (Weyer *et al*, 2001and Hotta *et al.*, 2001). During the early phase of atherosclerosis, circulating monocytes attach to injured endothelial cells through adhesion molecules and invade the subintimal space (Ross, 1993 and Hotta *et al.*, 2001). The monocytes transform into macrophages and secrete various cytokines and growth factors that promote smooth muscle cell proliferation. Adiponectin inhibits the expression of adhesion molecules and prevents the attachment of monocytes in TNF-α–stimulated human aortic endothelial cells (Ouchi *et al.*, 2000). This protein also dramatically suppresses the secretion of TNF-α from macrophages and foam cell formation (Ouchi *et al.*, 2001). These data suggest that adiponectin works as an anti-atherogenic molecule. Although its receptor has not been identified, adiponectin modulates NFκB signaling, at least partly, through a cAMP-dependent pathway. The plasma adiponectin concentration is decreased in insulin-resistant states, such as obesity and type 2 diabetes (Arita *et al.*, 1999). Kissebah *et al.* (2000) demonstrated two quantitative trait loci that influence the phenotypes of the insulin resistance–metabolic syndrome. One is located on chromosome 3q 27, where the adiponectin gene is encoded (Takahashi *et al.*, 2000). In light of these data, hypoadiponectinemia may play a role in the development of atherosclerotic vascular disease in patients with insulin resistance. The mechanisms that control the plasma adiponectin concentration have not been elucidated.

In the current study, we demonstrated a significant decrease in plasma adiponectin ($P < 0.01$) in diabetic patients, controlled

uncomplicated diabetes (G_I) and diabetes with hypertension and retinopathy (G_{II}) versus control. In diabetic patients with hypertension and retinopathy (G_{II}) there were significant decreases in plasma adiponectin levels ($P< 0.01$) and significant increases in fasting plasma glucose levels ($P< 0.05$) as compared to their levels in controlled uncomplicated diabetic patients (G_I) and control group. Our results also show that there were non-significant changes in plasma resistin levels in diabetic patients in both groups G_I & GII versus control group. These results are in agreement with those of Chen *et al*. (2005) who observed that plasma adiponectin was decrease in type 2 diabetic patients, while plasma resistin level did not differ between diabetic patients and control group. Baranova *et al.* (2006) observed that obese patients with insulin resistance have decreased serum adiponectin and increased serum resistin. Additionally, adiponectin gene expression is also decreased in the adipose tissue of these patients. Al-Harithy and Al-Ghamdi. (2005) also demonstrated that rsistin concentrations are elevated in patients with type 2 diabetes and are associated with obesity and insulin resistance. These data indicate that resistin might be involved in the development of diabetes in humans.

The mechanism responsible for the decreased adiponectin concentration in insulin resistance has been obscure. TNF-α is one of the candidate molecules responsible for causing insulin resistance (Hotamisligil *et al.*, 1995).The expression and secretion of adiponectin from adipocytes were significantly reduced by TNF-α in a dose- and time-dependent manner via its promoter activity. The expression of adiponectin mRNA was reduced in the adipose tissue of insulin-resistant obese humans and rodents, where TNF-α production was increased (Statnick *et al.*, 2000). Therefore, increased TNF-α might be partially responsible for the decreased adiponectin production in obesity. Hojlund *et al.* (2006) observed that plasma adiponectin was significantly reduced in type 2 diabetic compared with obese and lean subjects. In lean and obese subjects, insulin significantly reduced plasma adiponectin, but this response was blunted in patients with type 2 diabetes.: these results indicate that plasma adiponectin may enhance insulin sensitivity by improving the capacity to switch from lipid to glucose oxidation and to store glucose as glycogen in response to insulin, and that low adiponectin may contribute to impaired insulin activation of glycogen synthase (GS) in skeletal muscle of patients with type 2 diabetes.

Clinical aspects of diabetes and obesity are somewhat different, even at similar levels of insulin resistance. Factors involved in pathophysiology, including different serum adiponectin levels and body fat distributions, are believed to be responsible for differences in clinical characteristics, even at similar levels of insulin resistance in both diseases(Kim *et al.,* 2006). Plasma levels of adiponectin are lower in obese and insulin-resistant subjects compared with lean and insulin-sensitive ones. Thiazolidinediones increase plasma adiponectin levels in diabetic subjects, although the mechanism of this increased plasma adiponectin has not been well studied. Metformin did not cause any change in plasma or expression levels of adiponectin, but decreased plasma levels of resistin in impaired glucose tolerance subjects (Rasouli *et al.*, 2006). In contrast to other adipokines, resistin is only weakly associated with body fat and is unlikely to be a major mediator of insulin resistance or the metabolic syndrome in humans (Utzschneider *et al.*, 2005). In summary, higher adiponectin levels are associated with better glycemic control, more favorable lipid profile, and reduced inflammation in diabetic women (Mantzoros *et al.*, 2005).

Conclusion

The current study showed that plasma adiponectin levels were significantly reduced in obese type 2 diabetic patients and is even lower in those patients with hypertension and retinopathy, while plasma resistin level did not differ between diabetic

patients and control group. Our results suggest that adiponectin may play a key role in pathophysiology of type 2 diabetes mellitus and its microangiopathy and macro vascular complications.

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مستوى الاديبونكتن و الرزستن فى بلازما السيدات اللاتى تعانى من السمنة و السكري فى وجود وعدم وجود ضغط الدم العالى و أمراض الشبكية

سهام محمد سعيد النقيب*- منال عبد اللطيف **- أحمد محمد راغب *- عادل بلحه*****

بكر محمد عبد الله البو ****

قسما الكيمياء الحيوية* ، الباطنة العامة** كلية طب بنات -جامعة الأزهر

قسم الباثولوجية الإكلينيكية*** كلية طب بنين - جامعة الأزهر

كلية التقنية الطبية**** مسلاتة جامعة المرقب

مقدمه: لا يقتصر عمل الخلايا الدهنية على تخزين الدهون ولكنها تفرز الكثير من البروتينات و الهرمونات مثل الاديبونكتن و الرزستن وغيرها وهذة الهرمونات هى التى تنظم افراز و عمل الانسولين و من الممكن ان تكون هذة الهرمونات حلقة الاتصال بين السمنة والسكرى. ويهدف هذا البحث الى دراسة مستوى الاديبونكتن و الرزستن فى بلازما السيدات اللاتى تعانين من السكرى والسمنة في وجود و عدم وجود ضغط الدم العالي و أمراض الشبكية .

المرضي و الطرق: قد أجرى هذا البحث على 40 سيدة مصابة بمرض السكري قسمن إلى مجموعتين . المجموعة الأولى تضم عشرين سيدة تم تنظيم السكر لديهن و لا يعانين من مشاكل خطيرة ناتجة من مرض السكري . المجموعة الثانية تتكون من عشرون سيدة يعانين من ضغط الدم العالي و أمراض في شبكية العين و هذا بالإضافة إلى عشرون سيدة من الأصحاء اللاتي لا يعانون من أي مرض مزمن كمجموعة ضابطة .

النتائج: قد أظهرت النتائج نقص ذو دلالة إحصائية فى مستوى الاديبونكتن فى بلازما مريضات السكري فى المجموعتين عند مقارنتهم بالأصحاء فى المجموعة الضابطة . وقد أوضحت النتائج نقص ذو دلالة إحصائية فى مستوى الاديبونكتن فى مريضات السكري فى المجموعة الثانية و اللاتي يعانين من ضغط الدم العالي و أمراض في شبكية العين عند مقارنتهم بمريضات السكري فى المجموعة الأولى و اللاتي تم تنظيم السكر لكل منهن. وأظهرت النتائج أيضا أنة لا يوجد تغيرات لها دلالة إحصائية فى مستوى الرزستن فى بلازما مريضات السكري فى المجموعتين عند مقارنتهم بالمجموعة الضابطة .

الخلاصة: تشير هذه النتائج إلى ان الاديبونكتن له دور مهم في مرض السكري و مشاكله من زيادة في ضغط الدم و أمراض الشبكية.