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Evaluation of the serum visfatin and adiponectin levels in patients with type 2 diabetes mellitus

[Tip 2 diabetes mellitus'lu hastalarda serum visfatin ve adiponektin düzeylerinin değerlendirilmesi]

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ABSTRACT

Objective: The purpose of this study was to assess the levels of serum adiponectin and visfatin in patients with Type 2 Diabetes Mellitus and to investigate their potential roles in insulin resistance and obesity in T2DM.

Methods: The study was carried out in 45 patients with T2DM and 20 sex and age matched healthy control subjects (n=20). According to the body mass index (BMI) 45 patients were divided into two subgroups; one group was nonobese diabetic patients with 18.50 < BMI < 24.99kg/m^2 (n=20) and the other group was type 2 diabetic obese diabetic patients with BMI ≥30kg/m^2 (n=25). Serum adiponectin and visfatin levels were determined by using ELISA (Enzyme-Linked Immuno-Sorbent Assay) method. The insulin resistance index was assessed by homeostasis model assessment for insulin resistance (HOMA-IR).

Results: Serum adiponectin levels in obese and non-obese diabetic subjects was low when compared to the control group (p<0.001 and p<0.01; respectively). Conversely adiponectin, visfatin levels compared with control was higher in obese diabetic (p<0.001). When adiponectin was negatively correlated with duration of diabetes, body mass index, HOMA-IR, HbA1c, and glucose, visfatin was positively correlated with HOMA-IR and body mass index.

Conclusion: Diabetic patients compared with healthy control group decreased serum adiponectin and increased serum visfatin levels may be useful in the elucidation of the connection between obesity - insulin resistance.

Keywords: Adiponectin, adipose tissue, type 2 diabetes mellitus, visfatin

Conflict of Interest: The authors have declared that no conflict of interest exists.

ÖZET

Amaç: Bu çalışmadaki amaç Tip 2 diyabetlilerde serum adiponektin ve visfatin düzeylerini değerlendirmek, diyabette obezite ve insülin direncindeki potansiyel rollerini araştırmaktır.

Yöntemler: Bu çalışma yaş ve cinsiyet karşılaştırmalı 20 sağlıklı kontrol ve 45 Tip 2 diyabetli hastada gerçekleştirildi. Vücut Kütle İndeksine göre 45 hasta iki alt gruba ayrıldı; birinci grup Vücut Kütle indeksi 18.5 – 24.99 kg/m^2 olan 20 hasta ve diğer grup Vücut Kütle indeksi 30 kg/m^2 ve üzeri olan Tip 2 diyabetli 25 hasta. Serum adiponektin ve visfatin düzeyleri ELISA yöntemiyle belirlendi. İnsülin direnci homeostatik model değerlendirme indeksi (HOMA) ile değerlendirildi.

Bulgular: Serum adiponektin düzeyleri obez ve obez olmayan bireylerde kontrol grubuna göre karşılaştırıldığında düşüktü (sırasıyla; p<0.001 ve p<0.01). Adiponektinin tersine visfatin düzeyleri kontrollerle karşılaştırıldığında obez diyabetlilerde yüksek (p<0.001). Adiponektin diyabet süresi, vücut kütle indeksi, HOMA-IR, HbA1c ve glukoz değerleriyle negatif korelasyon gösterirken, visfatin vücut kütle indeksi ve HOMA-IR ile pozitif koraleydi.

Sonuç: Sağlıklı kontrol grubuyla karşılaştırıldığında azalan serum adiponektin ve artan serum visfatin düzeyleri diyabetiklerde obezite - insülin direnci arasındaki bağlantının aydınlatılmasında faydalı olabilir.

Anahtar Kelimeler: Adiponektin, adipoz doku, tip 2 diabetes mellitus, visfatin

Çıkar Çatışması: Yazarlar hiçbir çıkar çatışması bulunmadığını beyan eder.

Introduction

Type 2 Diabetes Mellitus (T2DM) is considered one of the major metabolic diseases of 21st century. The excessive food intake, sedentary life style, and lack of physical activity are responsible for the growing epidemic of obesity, together with the increasing rate of T2DM in many parts of the world. Type 2 Diabetes Mellitus arises from two defects: impaired insulin action and impaired β-cell function/insulin secretion of pancreas. Impaired insulin action (i.e., insulin resistance) occurs when target tissues are unable to respond to normal circulating concentrations of insulin.

The incidence of obesity has dramatically increased, and become epidemic in the western world. Obesity is a major risk factor for the development of several chronic diseases including T2DM. Obesity characterized by increased storage of fatty acids has an expanded adipose tissue mass and closely associated with the development of insulin resistance in peripheral tissues as skeletal muscle and the liver. Both obesity and T2DM are causally linked through their association with the development of insulin resistance.

Adipose tissue is a complex, essential, and highly active metabolic and endocrine organ. The classical perception of adipose tissue as a storage place of fatty acids has been replaced over the last years by the notion that adipose tissue has a central role in lipid and glucose metabolism and produces a large number of hormones and cytokines. These chemical messengers, collectively known as "adipocytokines or adipokines," include tumour necrosis factor alpha (TNF-α), adiponectin, leptin, resistin and visfatin [1]. Various signalling molecules secreted by adipocytes have been implicated in the development of insulin resistance and T2DM, based on results from animal models and metabolic studies in humans [2].

Adiponectin is the most abundantly expressed adipokine and differs from the other adipocytokines in that its concentrations decrease with increasing obesity and increase with weight loss [3]. Amount of adiponectin released increased with fat cell size and the levels of adiponectin decreased when BMI increased [4]. Adiponectin has been suggested to have insulin sensitizing, anti-inflammatory and anti-atherogenic effects [5, 6]. The strength and consistency of the relation between plasma adiponectin and risk of T2DM is unclear [7].

Visfatin, a new adipokine, was described recently and facilitates adipogenesis and has insulin-mimetic properties and reduces plasma glucose levels [8]. Visfatin is expressed in many cells and tissues and was previously identified as a protein involved in B-cell maturation (pre–B-cell colony-enhancing factor). Several clinical studies were conducted in order to analyse the validity of visfatin data and its relationship with insulin resistance, diabetes and obesity. However, there are controversies in the results of these studies [9, 10]. Other investigators have also found increased levels of visfatin in type 2 diabetic patients but failed to find a correlation between anthropometric measurements, lipid measures, fasting glucose, insulin resistance [11]. Therefore there are a number of disagreements among the different studies about visfatin and the role of this adipocytokines in obesity and insulin resistance is not clear.

We aimed to investigate the roles of adiponectin and visfatin levels on insulin resistance and obesity in Type 2 Diabetes Mellitus.

Materials and Methods

Study population

This study was conducted by cooperation of two departments: Department of Medical Biochemistry and Department of Endocrinology in Eskisehir Osmangazi University Faculty of Medicine in Turkey. The study was approved by ethical committee of Osmangazi University faculty of Medicine (2007/143).

Forty-five patients with Type 2 Diabetes Mellitus (males 20, females 25) were recruited from Department of Endocrinology. Control group was comprised of 20 volunteers (males 11, females 9) who did not have diabetes and other chronic diseases and compatible with patient group in terms age and sex. Type 2 Diabetes Mellitus subjects were included in the study according to American Diabetes Society criteria. Exclusion criteria was including active infection, positively of Hepatitis B and C, active liver disease, Familial Mediterranean Fever or acute infections, pregnancy and malignancy in both patients and controls.

Patients and controls were non-smokers. None of the individuals included in the study were using alcohol or taking vitamin supplements, other antioxidants and hormone replacement therapy.

All individuals in both patient and control group were informed about the study and their signed approvals were obtained. The some patients with T2DM were using ACE (Angiotensin-converting-enzyme) inhibitors (n=10), statins (n=8) and oral antidiabetic agents (n=45), but anybody was not applied insulin therapy.

Blood sample collection

In order to prevent interference, individual patients and controls were advised not to do heavy exercise, drink or smoke and eat anything prior to blood sampling. Venous blood samples were collected from an antecubital vein (7.00-9.00 a.m.) after a 12-h overnight fasting period, 10 ml of venous blood from each patients were sampled to biochemistry tubes with gel separator and to heparinised tubes for HbA1C (Haemoglobin A1C) measurements. Biochemistry tubes were centrifuged at 2000xg for 15 min after an incubation period of 30 min. Fasting glucose and HbA1C measurements were performed in the same day when serum were separated from blood samples. Remaining serum specimens were kept at -20°C until adiponectin and visfatin analyses were performed.

Biochemical analyses

Glucose levels were measured in a MODULER analyser using Roche Diagnostic kits by enzymatic colorimetric method. Insulin levels were measured by chemiluminescence method using IMMULITE-I analyser with DPC (Diagnostic Products Corporation Los Angeles, CA USA) kits. HbA1C levels were measured by turbidimetry immunoassay method using Hitachi 917 analyser with Roche Diagnostic kits.

Serum adiponectin levels were measured by Enzyme Linked Immunosorbent Assay (ELISA) using AviBion Human Adiponectin (Orgenium Laboratories, Helsinki) ELISA test kits. Adiponectin test was evaluated by intra-assay precision (≤10%, CV %) and inter-assay precision (<12%, CV %) according to the given information by kit manufacturer. Serum visfatin levels were measured by Enzyme Linked Immunosorbent Assay (ELISA) using Biosource Immunoassay test (Biosource International, Inc., USA) Human Visfatin ELISA test kits. Visfatin test was evaluated by intra-assay precision (7.76%, CV %) and inter-assay precision (7.97%, CV %) according to the given information by kit manufacturer. These sums did not repeat in our laboratory.

Calculation

Body mass index (BMI) was calculated by dividing the weight value of the patient to the square of height value. The estimate of insulin resistance by HOMA (homeostatic model assessment) score was calculated with the formula: fasting serum insulin (μU/ml) x fasting plasma glucose (mmol/l)/22.5. With such a method, high HOMA scores denote low insulin sensitivity (insulin resistance). Patients with T2DM were divided two subgroups according to current WHO classification of [12] BMI levels: 18.50 - 24.99 kg/m^2 was called nonobese type 2 diabetic and BMI ≥ 30 kg/m^2 was called obese type 2 diabetic.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) for Windows 19.0 package program (SPSS Inc., Chicago, IL, USA) was used to evaluate results. Kolmogorov-Smirnov test was done to evaluate the distribution of variables. Kruskal-Wallis and Mann– Whitney U tests were used to compare parameters, which do not show normal distribution, among groups. Pearson correlation test was used to investigate the relationships between parameters, which show normal distribution. Spearman correlation test was used to investigate the relationships between parameters, which do not show normal distribution. Results were accepted as significant for $p < 0.05$. Values are expressed as mean ± standard deviation (S.D.), median (25th percentiles-75th percentiles) where necessary.

Results

Clinical and biochemical features of patients and controls were presented in Table 1. Table 1 summarized the clinical and biochemical characteristics of controls and T2DM patients. Considering age, when nonobese and obese T2DM and controls are comparised, no difference was observed. However HOMA-IR (*p<0.001*), HbA1C (*p<0.001*), glucose (*p<0.001*) in both obese and nonobese T2DM groups were significantly higher than controls. BMI levels were increased in obese group compared with nonobese (*p<0.001*) and control (*p<0.001*) group.

The results of visfatin and adiponectin are shown in Figure 1 and 2, respectively. Serum adiponectin levels of nonobese and obese T2DM were decreased as compared to that in control group (*p<0.01* and *p<0.001*; respectively). Moreover adiponectin levels of obese diabetic patients were also lower than that nonobese but not significant for statistical (*p>0.05*). Serum visfatin levels of obese T2DM patients were increased as compared to that in controls (*p<0.001*) but visfatin levels of controls and nonobese T2DM patients, obese and non – obese T2DM patients was not different (*p>0.05*).

Table 2 represents the relationship between serum adiponectin and visfatin levels with age, glucose, DM duration, HOMA-IR, BMI in all T2DM groups (n=45). Serum adiponectin levels were negatively correlated with BMI, glucose, HOMA-IR, HbA1C whereas visfatin was only positively correlated with BMI and HOMA-IR.

Conclusion

In the present study, we measured total serum adiponectin and visfatin levels in T2DM patients that were divided into by BMI levels to investigate their relationship with obese and non-obese diabetics. There are unclear data concerning the role of these adipokines.

As a consequence of sustained over nourishment, obesity has become epidemic in worldwide. Obesity, especially visceral obesity, which is the accumulation of adipose tissue inside the abdominal cavity, is associated with resistance to the effects of insulin [IR (insulin resistance)], often leading to the development of T2DM. Type 2 Diabetes Mellitus is an important health problem since the incidence of T2DM is continuously increasing [13].

Although adipose tissue was regarded only stores energy until the last decade, it is now known as the largest endocrine organ of the body. Adipose tissue is an active tissue that secretes multiple metabolically important proteins called ‘adipokines’. Several studies have shown that the production of some adipokines such as adiponectin and visfatin is influenced in obesity and in type 2 diabetes.

Adiponectin is a 30-kDa protein that highly expressed in adipose tissue but a lot of studies show that its levels paradoxically decreased in obesity. In obese animals, treatment with adiponectin decreases hyperglycaemia and improves insulin sensitivity [14, 15]. Furthermore, adiponectin-deficient mice develop diet-induced IR on a high-fat/high-sucrose diet [16]. In humans, plasma levels of adiponectin are significantly lower in insulin-

Table 1. Demographic and laboratory datas of obese and nonobese type 2 diabetic patients and controls

		Type 2 Diabetic Patients		
	Control	Non-obese	Obese	*p* value
n	20	20	25	
Male/Female Ratio	11/9	11/9	12/13	
Age (years)	57.55 ± 11.31	63.30 ± 9.29	60.64 ± 11.87	ns
BMI (kg/m^2)	25.45 ± 2.86	23.66 ± 0.96	31.45 ± 3.36	$p < 0.001^{a,c}$
DM duration (years)	---	10.00 (5.25 - 14.75)	12.00 (6.00 – 16.00)	*ns*
Glucose (mg/dl)	83.50 (76.75-86.75)	211.50 (142.00 -228.75)	201.00 (133.00 -257.00)	$p < 0.001^{a,b}$
HbA1c (%)	4.55 (4.00 - 5.20)	7.06 (6.70 - 8.34)	7.70 (6.74 - 8.82)	$p < 0.001^{a,b}$
HOMA-IR	1.55 ± 0.68	4.04 ± 2.22	5.72 ± 3.11	$p < 0.001^{a,b}$

Values are expressed as means ± SD or medians (25th - 75th percentiles), BMI, Body Mass Index, HbA1c, haemoglobin A1c, HOMA-IR, homeostatic model assessment index,
ns; not significant,
a; obese versus control,
b; non-obese versus control,
c; obese versus non-obese

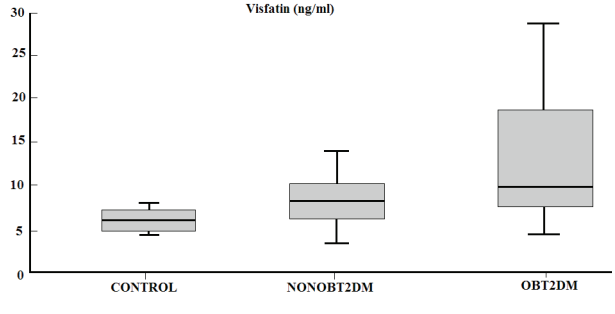

Figure 1. A Boxplot illustration of serum visfatin concentrations in subjects of Type 2 Diabetes Mellitus obese (n=25) and nonobese (n=20) patients and healthy controls (n=20). NonObT2DM; nonobese Type 2 Diabetes Mellitus, ObT2DM; obese Type 2 Diabetes Mellitus

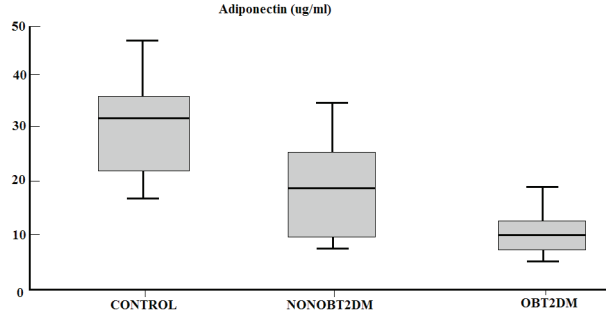

Figure 2. A Boxplot illustration of serum adiponectin concentrations in subjects of Type 2 Diabetes Mellitus obese (n=25) and nonobese (n=20) patients and healthy controls (n=20). NonObT2DM; nonobese Type 2 Diabetes Mellitus, ObT2DM; obese Type 2 Diabetes Mellitus

resistant states including type 2 diabetes [17] and can be increased upon administration of the insulin-sensitizing agents by Thiazolidinedione or TZDs, also known as glitazones, that act by activating PPARs (peroxisome proliferator-activated receptors) [18-21].

We found that serum adiponectin levels of healthy control group were conspicuously higher than obese and nonobese diabetics. Although adiponectin levels of diabetic non-obese group were higher than the obese group but this elevation was not statistically significant. So that, there was no differences between diabetics groups. Although adiponectin was negatively correlated with BMI as a convenient calculator of obesity, it is apparent from our study of obese and nonobese diabetic individuals adiponectin levels looks like more tightly linked with insulin resistance when we look at the correlation table. Altınova et al. [22] resulted that circulating adiponectin is associated with insulin resistance independent from BMI in overweight subjects.

Decreased adiponectin levels in type 2 diabetes may be one of the reasons to cause insulin resistance [23]. The HOMA model is used to quantify insulin resistance and beta-cell function from fasting plasma insulin and glucose concentrations [24]. The relationship between glucose and insulin in the basal state reflects the balance between hepatic glucose output and insulin secretion, which is regularized by a feedback circuit between the liver and β-cells. Numerous studies [25] showed that adiponectin improved insulin sensitivity mainly by increasing fatty acids oxidation and inhibition of hepatic glucose production by stimulatory effects of adiponectin on signalling pathways for 5′ adenosine monophos-

Table 2. Correlations between serum adiponectin and visfatin levels with demographic and laboratory datas of all type 2 diabetic patients (n=45)

	Adiponectin		Visfatin	
	r	p	r	p
Age (years)	-0.203	0.180	0.060	0.674
DM duration (years)	**-0.228**	**0.013**	0.156	0.300
BMI (kg/m^2)	**-0.628****	**0.001**	**0.301***	**0.045**
HOMA-IR	**-0.468****	**0.001**	**0.458****	**0.002**
HbA1c (%)	**-0.390****	**0.008**	0.137	0.371
Glucose (mg/dl)	**-0.316***	**0.035**	-0.041	0.791

BMI, Body Mass Index, HOMA-IR, Homeostasis Model of Assessment Index, HbA1c, haemoglobin A1c
** $p<0.01$
* $p<0.05$

phate–activated protein kinase and peroxisome proliferator–activated receptor α. In our study, adiponectin levels that negatively correlated with HOMA rather than adiposity in which that high HOMA-IR value indicates low insulin sensitivity (insulin resistance) may be an extremely important for type 2 diabetes which is an indicator predicting development of insulin resistance in terms of early diagnosis can give important insight.

The association between adiponectin levels and the 6-year risk of type 2 diabetes in a population of 2500 older white men and women were investigated by The Hoorn Study [26] and this study showed that a lower adiponectin level associated with a higher risk of type 2 diabetes. In the British Regional Heart Study (BRHS) showed that, men with adiponectin concentrations in the top tertile (vs. the bottom tertile) had a 60% lower risk of incident type 2 diabetes after 5 years [27]. These results are shown an inverse correlation between the adiponectin concentration and the duration of diabetes and this correlation is also confirmed in our results. We have observed that adiponectin may have a central role in the pathogenesis of T2DM and low adiponectin concentration may be a candidate messenger of future development of T2DM in subjects with obesity compared to healthy.

These effects may be in part mediated by the level of expression of both the AdipoR1 and AdipoR2 receptors [28] and the distribution of the HMW (High Molecular Weight isomer of Adiponectin) and LMW (Low Molecular Weight isomer of Adiponectin) isoforms of adiponectin may play a role in insulin sensitivity [29]. The negative correlation with BMI may be a good indicator about obesity related insulin resistance in T2DM, but in obese and non-obese type 2 diabetic groups, failure to establish the their inverse relationship may be attributed partially by other hormones such as catecholamines or androgen, by proinflammatory cytokines such as TNF-α, by medications, by insulin levels, or possibly by changes in clearance of adiponectin [30].

Visfatin is expressed in many cells and tissues, and was previously recognized as a Pre-B Cell Colony Enhancing Factor (PBEF). In recent times, visfatin was described to be a highly expressed protein with insulin-mimetic functions, and was predominantly found in visceral adipose tissue [31]. There are numerous incompatibilities among the different studies of visfatin, and the role of this adipokine in obesity and insulin resistance is not clear.

In the current study, we found that serum visfatin concentrations were significantly higher in the diabetic obese compared with the control group and diabetic groups showed a significant positive correlation with measures of obesity with BMI in opposition to adiponectin. In accordance with our results, Berndt et. al.[32] and Varma et. al. [33] found a significant positive correlation between visfatin levels and BMI.

In our results, diabetic patients showed a significant positive correlation between serum visfatin concentrations and HOMA-IR; in accordance with the results of Sandeep et al. [34], who found a strong correlation between serum visfatin and HOMA.

We showed that an elevated visfatin level in patients with T2DM, and suggests that this phenomenon is not prejudiced by the extent of overweight/obesity. In normal participants, plasma visfatin is increased with elevated blood glucose by the glucose clamp test [35]. On the basis of this disclosure, our results may support the idea that elevated visfatin in patients with T2DM may be a consequence of the hyperglycaemia conditions.

The present study seems to have some limitations. First, the sample size was small to represent all people with T2DM. Second, we estimated insulin resistance using HOMA-IR model for which some limitations were reported [24]. In this study, our analyses are based on single measurements of blood visfatin and adiponectin, which may not reflect the relationship over time. It would be interesting to measure serial changes of visfatin and adiponectin levels in obese, insulin resistant

subjects clarify further, the roles of visfatin and adiponectin in the pathogenesis of T2DM. On the other hand variation levels that related to intra- and inter- individuals have not been estimated. Due to unknown biological variation, evaluation of the difference has not been considered. Therefore, in order to be able to say different, the need for the determination of the existence of this concept should not be ignored.

In conclusion that increased body weight is tightly associated with insulin resistance and Type 2 Diabetes Mellitus. The roles of various adipokines as connectors between obesity and diabetes mellitus have been better elucidated in recent times. On the basis of this study finding, adiponectin and visfatin levels can be associated with insulin sensitivity at obese diabetic patients compared to healthy control. Future prospective studies with greater numbers of patient are recommended to establish a direct relationship between serum adiponectin and visfatin concentrations.

Conflict of interest: The authors have declared that no conflict of interest exists.

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