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Comparison of Adiponectin Values in Obese and Nonobese Diabetics and Relationship with Metabolic Parameters

Obez ve Nonobez Diyabetiklerde Adiponektin Düzeylerinin Karşılaştırılması ve Metabolik Parametrelerle İlişkisi

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SUMMARY

Objectives: *Adipose tissue stores energy and acts as an active endocrine organ that secretes adiponectin. It is noted that adiponectin level is decreased in obesity and metabolic syndrome. The aim of this study was to measure the adiponectin levels of obese and non-obese patients previously diagnosed with type-2 diabetes and to evaluate the relationship of adiponectin with other metabolic parameters.*

Methods: *The study included 46 obese and 38 non-obese diabetic patients who were admitted to the Diabetes and Endocrinology Clinics of our hospital. Their anthropomorphic and metabolic parameters were measured and were compared to the adiponectin levels. Fasting blood glucose, postprandial blood glucose, urea, creatinine, total protein, albumin, total cholesterol, LDL, HDL, triglyceride and* HbA_{1c} *levels were measured spectrophotometrically. Insulin levels were measured through electrochemiluminescence. Adiponectin was measured by sandwich ELISA technique.*

Results: *Our study revealed that obese type-2 diabetic patients showed lower adiponectin levels in comparison to non-obese ones (p=0.0001). It was shown that the insulin resistance and waist circumference increased while adiponectin levels decreased. It was found that these were the two key parameters determining adiponectin levels.*

Conclusion: *We conclude that adiponectin which increases insulin sensitivity and is known to have anti-inflammatory and anti-atherogenic properties, was found to be lower in obese diabetics as compared to non-obese diabetics and this can be a factor increasing the risk of atherosclerosis.*

Key words: *Adiponectin; adipose tissue; metabolic parameters; obesity; type-2 diabetes mellitus.*

ÖZET

Amaç: Yağ dokusu enerji depolayan ve adiponektin salgılayan aktif bir endokrin organ olarak çalışır. Adiponektin düzeylerinin obezite ve metabolik sendromda azaldığı farkedilmiştir. Bu çalışmanın amacı, obez ve obez olmayan tip 2 diyabetli hastalarda adiponektin düzeylerinin ölçülmesi ve bunun diğer metabolik parametrelerle ilişkisinin değerlendirilmesidir.

Gereç ve Yöntem: Çalışmaya hastanemiz diyabet ve endokrinoloji polikliniklerine başvuran 46 obez, 38 obez olmayan hasta alındı. Antropometrik ve metabolik değişkenleri adiponektin düzeyleri ile karşılaştırıldı. Hastaların açlık kan şekeri, tokluk kan şekeri, üre, kreatinin, toplam protein, albümin, toplam kolesterol, LDL-kolesterol, HDL-kolesterol, trigliserid, HbA_{1c} değerleri spektrofotometrik yöntemle ölçüldü. İnsülin düzeyleri elektrokemilüminesans, adiponektin ise sandviç-ELISA yöntemi ile ölçüldü.

Bulgular: Çalışmamızda obez tip 2 diyabetiklerin obez olmayanlara göre daha düşük adiponektin düzeylerine sahip olduğu görüldü (p=0.0001). Adiponektin düzeyleri düştükçe insülin direncinin ve bel çevresinin arttığı saptandı. Bu iki ölçütün adiponektin düzeyini tayin eden ana parametre olduğu gözlendi.

Sonuç: İnsülin duyarlılığını arttıran antiyaterojenik ve antienflamatuvar özellikleri olan adiponektin obez diyabetiklerde obez olmayanlara göre düşüktür ve bu durum ateroskleroz riskini arttıran bir faktör olabilir.

Anahtar sözcükler: Adiponektin; yağ dokusu; metabolik parametreler; obezite; tip 2 diabetes mellitus.

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INTRODUCTION

Adipose tissue is a large and active endocrine organ beyond storing energy and having lipolytic activities. It secreting proteins called adipocytokines that affect glucose metabolism, inflammation, energy balance, lipid metabolism, fibrinolytic system, and vascular homeostasis.[1,2] It is thought that through these effects, they are involved in complications like hyperlipidemia, diabetes mellitus (DM), arterial hypertension, atherosclerosis and heart failure which are related to obesity. Numerous substances like leptin, resistine, tumor necrosis factor-alpha (TNFα), adiponectin, interleukin-6 (IL-6), monocyte chemoattractan protein-1 and plasminogen activator inhibitor-1 are released from the adipose tissue.[3,4] One of these substances; adiponectin, is an antidiabetic and antiatherogenic protein and its concentration decreases in obesity-related metabolic and vascular diseases.[3] Adiponectin level is associated with insulin sensitization, glucose use, beta oxidation, hypertension and cardiovascular protection.

Obesity and obesity-related diseases play an important role in clinical medicine. The presence of abdominal and visceral obesity is often paired with insulin resistance leading an increase in the vascular complications of diabetes. Insulin resistance is a key factor in the pathogenesis of type 2 diabetes and is related to dyslipidemia, obesity and hypertension.[2,4,5]

In obese patients, adiponectin level decreases while the levels of leptin, resistine, TNFα, and IL-6 increase. Adiponectin is a plasma protein 30 kDa in mass[4] that is suggested to be protective against atherosclerosis and it is thought that this cytokine acts as an endogenous regulator of endothelium cells' response to inflammatory stimulants.[5-7]

Previous studies found low adiponectin levels in type 2 diabetic and obese patients. Some studies have investigated the relationship between adiponectin level and high-density lipoprotein (HDL), low-density lipoprotein (LDL), hemoglobin A_{1c} (HbA_{1c}), C-reactive protein (CRP), body mass index (BMI), fasting blood glucose (FBG) and postprandial blood glucose (PPBG). It was shown that patients with good glycemic control had higher adiponectin levels and adiponectin was a good indicator of metabolic control and atherosclerotic risk.[2,8,9]

The aim of this study was to measure the adiponectin levels of obese and nonobese patients previously diagnosed with type 2 diabetes and to evaluate the relationship of adiponectin with other metabolic parameters.

MATERIAL AND METHODS

The study included 46 obese and 38 nonobese type 2 diabetic patients who were admitted to Outpatient Clinics of Diabetes and Endocrinology between May and September 2008. Our study was conducted according to the principles expressed in the Declaration of Helsinki.All patients gave informed consent. The approval of the hospital ethics board was obtained.

Height, weight, waist circumference, BMI, systolic blood pressure (SBP) and diastolic blood pressure (DBP) of the patients were measured. Their age, duration of diabetes and medicine usage as well as personal and family history were noted.

The measurements and examinations were carried out by the same physician. BMI was calculated by the formula: Weight (kg)/Height^2 (m^2). Normal BMI was taken as 18-25 kg/m^2. Patients with BMI values of 25-30 kg/m^2 were classified as overweight; and those with BMI $\geq$30 kg/m^2 were considered obese.

Waist circumference (cm) was measured parallel to the midpoint between the lower limit of the 12th costa and the ischial spine. The limits were accepted as >102 cm in men, and >88 cm in women (ATP: adult treatment panel III criteria).

Homeostasis model assessment (HOMA) was used to detect insulin resistance (IR). HOMA-IR was calculated by the formula: Insulin (μU/ml)xFBG (mg/dl)/405.

Patients with history of stroke, transient ischemic attack (TIA), uncontrolled hypertension, or cardiovascular, liver, renal, thyroid, or any other serious diseases requiring active treatment; and patients using telmisartan, irbesartan or PPAR-γ agonists like rosiglitazone or pioglitazone which are known to affect adiponectin levels were excluded from the study.

Blood samples were collected following a 12-h fasting, and all the tests except adiponectin were performed on the same day. Fasting blood glucose (FBG), second hour postprandial blood glucose (2-h PPBG), urea, creatinine, total protein (T. protein), albumin, total cholesterol (T. cholesterol), LDL, HDL, triglyceride, and HbA_{1c} levels were measured spectrophotometrically in Abbott Aeroset Autoanalyzer.

Insulin, FT4, and TSH levels were measured by Roche E170 Autoanalyzer through electrochemiluminescence. Microalbuminuria levels in spot urine were tested turbidimetrically by Saturno Autoanalyzer. CRP levels were measured by nephelometry.

The blood sample collected to measure adiponectin was let to rest in the tube for coagulation, then it was placed into centrifuge for 10 minutes at 5000 g; and the resulting serum was preserved at -80°C. Serum adiponectin levels were measured with a commercial kit (AssayMax Human Adiponectin ELISA Kit, cat no: EA2500-1) using the sandwich ELISA technique in ELX 800 UV ELISA reader.

NCSS 2007 package was used for the statistical evaluation of the findings. Besides using descriptive statistical methods (mean, standard deviation) to evaluate the data, independent t-test for paired samples, and chi-square for qualitative data were employed. Stepwise linear regression analysis was used for the variables related to adiponectin levels.

RESULTS

The mean age of patients was 52.35±7.41 in the obese group and 55.0±57.7 in the nonobese group. There was no statistically significant difference in age (p=0.106).

There was no statistically significant difference between the obese and nonobese groups in gender (p=0.604).

The patients' data is shown in the Table 1, 2, 3.

Stepwise linear regression analysis was used with adiponectin values and the variables BMI, waist circumference, FBS, HDL, insulin, and HOMA-IR. Amongst these, only HOMA-IR and waist circumference were significant (p=0.0001, p=0.01). An increase in HOMA-IR and waist circumference values correlated with a decrease in adiponectin levels. It was determined that, when only insulin resistance was measured through HOMA-IR, 59% of the patients (R=0.589) would display low adiponectin levels; whereas when waist circumference was factored in with insulin resistance, the rate was 63% (R=0.631) (Table 4).

DISCUSSION

Evidence from animal and human studies show that adiponectin plays an important role in insulin resistance,[6,10-12] inflammation,[13] atherogenesis[2,5,14,15] and lipid metabolism[9,14,15] Different adiponectin levels in different ethnic groups were reported.[12] It was also measured in the plasma of healty volunteers in the range of 1.9-17.0 mg/ml. The obese patients had lower levels of adiponectin than the nonobese subjects.[16] Our study also revealed that adiponectin levels were lower in the obese diabetic group (9.32±2.07 µg/ml) than the nonobese diabetic group (11.12±1.66 µg/ml). Shand et al found that among metabolic syndrome patients without diabetes, adiponectin levels were higher in women than in men[14] Although some other studies found similar results,[14,15,17,18] there was no difference in our study with regard to gender.

Table 1. Clinical data of patients

	Nonobese	Obese	t	p
Duration of diabetes (years)	7.55±5.22	7.76±7.67	-0.14	0.887
Height (cm)	161.21±7.74	163.7±9.67	-1.28	0.204
Weight (kg)	67.89±7.68	91.91±15.83	-8.55	0.0001
Waist circumference (cm)	91.71±8.49	109.43±10.44	-8.41	0.0001
BMI kg/m^2	26.63±2.2	34.72±5.76	-8.17	0.0001
SBP (mmHg)	131.05±24.91	136.63±22.63	-1.07	0.286
DBP (mmHg)	77.11±13.54	83.7±14.35	-2.15	0.035

Table 2. Laboratory parameters of patients

	Nonobese	Obese	t	p
FBS (mg/dl)	166.47±72.94	183.24±66.49	-1.10	0.274
PPBS (mg/dl)	220.87±98.58	242.28±97.07	-1.00	0.321
Urea (mg/dl)	32.11±12.28	32.59±12.39	-0.18	0.859
Creatinine (mg/dl)	0.96±0.19	0.96±0.42	0.03	0.980
T. protein (g/dl)	7.5±0.34	7.51±0.42	-0.13	0.898
Albumin (g/dl)	4.69±0.46	4.57±0.46	1.22	0.228
T. cholesterol (mg/dl)	219.24±49.67	203.35±53.08	1.41	0.164
LDL (mg/dl)	134.82±42.1	125.43±44.76	0.98	0.329
HDL (mg/dl)	46.34±11.79	41.35±10.53	2.05	0.044
Triglyceride (mg/dl)	203.03±109.78	240.35±252.91	-0.85	0.400
CRP (mg/dl)	0.51±0.46	1.4±3.05	-1.79	0.077
Microalbuminuria (mg/dl)	72.17±87.35	66.02±62.34	0.38	0.708
HbA_{1c} (%)	7.95±1.88	8.16±1.95	-0.52	0.605
Insulin (µU/ml)	11.23±10.48	19.12±16.58	-2.54	0.013
HOMA	4.28±3.67	8.66±7.91	-3.14	0.002
FT4 (ng/dl)	1.29±0.18	1.33±0.18	-0.96	0.341
TSH (µU/ml)	1.71±1.19	1.99±1.16	-1.06	0.293
Adiponectin (µg/ml)	11.12±1.66	9.32±2.07	4.33	0.0001

Table 3. Correlation between adiponectin level and other parameters

		Adiponectin			Adiponectin
Age	r	0.19	Albumin	r	0.151
	p	0.083		p	0.171
Duration of diabetes	r	0.041	T. cholesterol	r	0.165
	p	0.708		p	0.133
Height	r	-0.128	LDL-cholesterol	r	0.15
	p	0.246		p	0.173
Weight	r	-0.406	HDL-cholesterol	r	0.261
	p	0.0001		p	0.016
Waist circumference	r	-0.417	Triglyceride	r	-0.022
	p	0.0001		p	0.84
BMI	r	-0.344	CRP	r	-0.123
	p	0.001		p	0.266
SBP	r	-0.108	Microalbuminuria	r	0.003
	p	0.33		p	0.982
DBP	r	-0.075	HbA_{1c}	r	-0.205
	p	0.498		p	0.061
FBS	r	-0.29	Insulin	r	-0.501
	p	0.007		p	0.0001
PPBS	r	-0.192	HOMA	r	-0.589
	p	0.081		p	0.0001
Urea	r	0.02	FT4	r	-0.094
	p	0.859		p	0.397
Creatinine	r	0.09	TSH	r	-0.017
	p	0.418		p	0.879
T. Protein	r	0.018			
	p	0.872			

Table 4. Stepwise linear regression analysis of the adiponectin variable

Model	R	R Square	Adjusted R Square	p
1	0.589a	0.346	0.338	0.0001
2	0.631b	0.398	0.383	0.01

	B	SE	Beta	t	p
(Constant)	15.108	1.45		10.42	0.0001
HOMA	-0.158	0.029	-0.505	-5.49	0.0001
Waist circumference	-0.039	0.015	-0.241	-2.627	0.01

We found a statistically significant negative correlation between adiponectin levels and both waist circumference and BMI (p=0.0001, p=0.001). Our findings were in accordance with the literature.[7,14,15,19,20] For the inflammation indicator CRP, no statistically significant difference was found between the obese and nonobese patients in our study. Nayak et al.[17] and Lautamaki et al.[20] could not either demonstrate a correlation between adiponectin and CRP levels whereas plasma adiponectin levels were suggested to correlate inversely with CRP and might act as an intermediate between CRP and diabetes.[7,8,14,19]

Weyer et al.[12] investigated the relationship between hypoadiponectinemia and both insulin resistance and hyperinsulinemia among type 2 diabetic and obese patients. Negative correlation was detected between plasma adiponectin concentration and body fat, waist-hip ratio, insulin levels, and PPBS. He also found that the degree of hypoadiponectinemia was more closely related to the degree of insulin resistance than the degree of adiposity which is similar to our results. There was a statistically relevant negative correlation between adiponectin levels and both insulin level and insulin resistance (p=0.0001) in our research.

In a study, Matsubara et al.[21] found that adiponectin levels were negatively correlated with fasting insulin, insulin resistance, BMI and body fat mass in nondiabetic Japanese women. In another study conducted on 967 Japanese subjects of normal weight, Yamamato et al found negative correlation between plasma adiponectin and BMI, systolic blood pressure, diastolic blood pressure, FBG, insulin level, insulin resistance, T. cholesterol, LDL, triglycerides, and uric acide.[15] Stejskal et al.[18] observed the adiponectin level as a criterion of metabolic control in patients with type 2- DM.

Many studies showed that adiponectin correlated negatively with BMI, FBG, uric acid, triglyceride, apolipoprotein B-100 and HbA_{1c} and positively with HDL. Adiponectin concentrations were higher in patients with good glycemic control and it was concluded that adiponectin is a good indicator of metabolic control and atherosclerotic risk.[8,14,18] When we compared obese and nonobese diabetic patients' FBG, 2-h PPBG, urea, Cr, T. protein, albumin, T. cholesterol, LDL, HDL, triglyceride and microalbuminuria values, we also found that the mean HDL value in obese patients was slightly, yet significantly, lower than the nonobese group (p=0.04); but no difference was found between other variables.

Low adiponectin levels may play a role in the pathogenesis of hypertension. Adiponectin level was negatively associated with systolic and diastolic blood pressure.[4,22] The effect of adiponectin on hypertension may be indirect.[15] We could not demonstrate a relationship between adiponectin levels and SBP or DBP.

Previous studies suggest that adiponectin has anti-hyperglycemic, anti-atherogenic and anti-inflammatory properties.[3,6,7,11,15] High serum adiponectin levels are related to high insulin sensitivity and glucose tolerance. Therefore, it is thought that adiponectin or drugs that stimulate the effects or the secretion of adiponectin may be effective in the treatment of type 2 DM and obesity-related diseases. Adiponectin supplementation and agents that could increase adiponectin levels and/or up- regulate Adipo R1 and Adipo R2 receptors may be new therapeutic alternatives when added to lifestyle modifications and other antidiabetic drugs.[7,21,23]

When stepwise linear regression analysis was used with adiponectin values and the variables BMI, waist circumference, FBG, HDL, insulin and HOMA-IR, it was observed that HOMA-IR and waist circumference values were statistically significant (p=0.0001,

p=0.01). It was reported that these were the two variables determining adiponectin levels and that they could act as the predictors for adiponectin decrease. [12,14,21]

There are some limitations of our study. *i)* The groups are small. *ii)* We did not evaluate healthy controls therefore we do not know our normal population's adiponectin level. *iii)* We did not divide the groups according to gender while investigating for BMI and WHC. This may be the reason why our nonobese group's waist circumference seems as high as the obese group. *iv)* Many drugs are known to affect adiponectin values. Most of our patients were using agents which are reported to increase adiponectin levels.[2,4] We could not exclude them and we did not seperate the groups according to the antidiabetic, antihypertensive or antilypemic drugs in order not to make the groups smaller.

CONCLUSION

Adiponectin is a cytokine secreted by the adipose tissue; and many studies show that hypoadiponectinemia plays a role in insulin resistance and the development of diabetes. It can be concluded that the lower adiponectin level in obese diabetics, in comparison to nonobese ones, is another factor that increases the atherosclerotic risk. Adiponectin can be seen as a promising and applicable means due to its anti-inflammatory and anti-atherogenic properties and its ability to increase insulin sensitivity. Further studies are needed to use adiponectin in the diagnosis and treatment of patients with obesity, insulin resistance, cardiovascular diseases, or metabolic syndrome.

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