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Low Serum Adiponectin Levels in Children and Adolescents with Diabetic Retinopathy

Diyabetik Retinopatili Çocuk ve Ergenlerde Düşük Serum Adinopektin Düzeyleri

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Abstract

Objective: The aim of this study was to elucidate the role of adiponectin, leptin, TNF-α and IL-6 on the early detection of the microvascular complications of type I diabetes.

Materials and Methods: A total of 88 children were included in the study. There were 60 type I diabetic patients and 28 healthy control children.

Results: The gender, age, weight, height, BMI and puberty status characteristics were similar in the patient and control groups (p>0.05). The serum leptin, TNF-α and IL-6 levels were similar between the patient and control groups (p>0.05) and the only difference was in the serum adiponectin level which was higher in the patient group (p:0.042). We also found no association between the adiponectin, leptin, TNF-α and IL-6 levels and diabetes duration (p>0.05). Leptin was high in the pubertal period (p:0.016), while adiponectin TNF-α and IL-6 levels were similar in the prepubertal and pubertal periods (p>0.05). The serum leptin level was high in microalbuminuria patients (p<0.041). The serum adiponectin, TNF-α, and IL-6 levels were not different in patients with and without microalbuminuria (p>0.05). The serum adiponectin level was lower in diabetic retinopathy patients (p:0.003), while the serum leptin level was higher (p:0.003). The TNF-α and IL-6 levels were similar in patients with and without retinopathy (p>0.05).

Conclusion: We found increased serum adinopectin levels in children and adolescents with type I diabetes mellitus and low levels in diabetic retinopathy patients. Patients with low serum adiponectin levels and high leptin levels should be more closely monitored for chronic complication development and better metabolic control should be aimed for.

Key Words: Adinopectin, Children and Adolescents, Leptin, Retinopathy, Type I Diabetes Mellitus

Özet

Amaç: Bu çalışmada tip I diyabetin mikrovasküler komplikasyonlarının erken saptanması ve bu komplikasyonların erken tanınmasında adiponektin, leptin, TNF-α ve IL-6'nın rolünün ortaya çıkarılması amaçlanmıştır.

Gereç ve Yöntem: Çalışmaya toplam 88 çocuk alınmıştır. Bunların 60'ı tip I diyabet'li hasta, 28'i sağlıklı kontrol çocuktan oluşmaktaydı.

Bulgular: Hasta ile kontrol grubu arasında cinsiyet, yaş, ağırlık, boy, VKİ, puberte durumları benzerdi (p>0.05). Hasta ile kontrol grubu arasında sadece serum adiponektin düzeyinin hasta grubunda daha yüksek olduğu saptanırken (p:0.042), hasta ile kontrol grubu arasında serum leptin, TNF-α ve IL-6 düzeyleri benzerdi (p>0.05). Diyabet süreleri ile adiponektin, leptin, TNF-α ve IL-6 düzeyleri arasında da bir ilişki saptanmadı (P>0.05). Puberte döneminde leptin yüksekliği saptanırken (p:0.016), adiponektin, TNF-α ve IL-6 düzeyleri prepubertal ve pubertal dönemde benzerdi (p>0.05). Mikroalbuminürili hastalarda serum leptin yüksekliği saptanırken (p<0.041), serum adiponektin, TNF-α ve IL-6 düzeyleri mikroalbuminüri olan ve olmayan hastalarda benzerdi (p>0.05). Diyabetik retinopatili hastalarda serum adiponektin düzeyi daha düşük (P:0.003), serum leptin düzeyi daha yüksek saptandı (p:0.003). TNF-α ve IL-6 düzeyleri retinopati olan ve olmayan hastalarda benzerdi (p>0.05).

Sonuç: Tip 1 diyabetli çocuk ve adolesanlarda serum adinopektin düzeyini artmış olarak bulurken diyabetik retinopatili hastalarda ise bu düzeyi düşük bulduk. Serum adiponektin düşüklüğü ve leptin yüksekliği olan hastalar kronik komplikasyonların gelişimi açısından daha yakın takip edilmeli ve daha iyi bir metabolik kontrol sağlanmaya çalışılmalıdır.

Anahtar Kelimeler: Adinopektin, Çocuk ve Ergen, Leptin, Retino, Tip 1 Diyabet Mellitus

Introduction

The chronic complications observed in diabetes mellitus (DM) occur by angiopathic mechanisms and appear 10-20 years after the disease first develops. Early findings of late-stage complications, such as nephropathy, retinopathy, neuropathy, macroangiopathy and microangiopathy, start in childhood, and these complications can be either prevented or delayed with good metabolic control. Recognizing the long-term complications of diabetes in their early stages of development is thereforöe critical to increasing survival and improving the quality of life of diabetic patients [1, 2].

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Diabetic retinopathy is the most common complication of type I diabetes. It is usually not seen in the first 5-10 years. Only 20-30% of background retinopathy develops during the first 10-15 years of the disease, whereas 70-80% develops after 15 years The EURO DIAB prospective complications study found a 56% retinopathy incidence over 7 years of follow-up in 764 patients who were older than 15 years. Zhang et al. reported that the incidence of diabetic retinopathy was 10% with good metabolic control but greater than 40% without good metabolic control [3].

Adiponectin is a hormone that is synthesized in the adipose tissue and plays an important role in hyperglycemia, dyslipidemia and inflammatory mechanisms. Low adiponectin levels, in addition to insulin resistance, have been shown in type II diabetes, and adiponectin has been demonstrated to play an important role in the response to insulin. Adiponectin also shows anti-inflammatory and antiatherogenic properties [4, 5].

The aim of this study was to elucidate the role of adiponectin, leptin, TNF-α and IL-6 in detecting the microvascular complications of diabetes and to determine their relationship with the chronic diabetic complications.

Materials and Methods

Sixty type I diabetic patients were enrolled from the Cukurova University Medical Faculty, Pediatric Endocrine and Metabolism Outpatient Department. The control group consisted of 28 children in good health. Of the type I DM patients, those who were diagnosed 5 or fewer years prior to the study were compared to those who were diagnosed more than 5 years prior to the study, and the prepubertal patients were compared to the pubertal patients.

The duration of DM was noted for all patients who were included in the study. Blood pressure was measured with a mercury manometer, and fasting serum glucose, C-peptide, triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol and HbA1c levels were also measured.

In addition, 24-hour urine samples were collected, and the microalbuminuria levels and the urinary albumin excretion rate (AER) within the last year were calculated. Based on the urine samples, the patients were classified as follows: a group with no microalbuminuria in any of the 3 samples collected 24 hours apart; an intermittent microalbuminuria group, which showed levels of albumin over 20 µg/kg in only one of the three samples; and a persistent microalbuminuria group, which showed albumin levels of greater than 20 µ/kg in at least two of the three samples.

The retinopathy eye examination in all patients was performed by an experienced ophthalmologist with indirect fundus examination using a 90 Diopter Volk lens. We considered the presence or absence of retinopathy as the basis of our study; however, the retinopathy was not graded.

Serum was collected from all patients included in the study and stored at -70°C until adiponectin, leptin, TNF-α and IL-6 measurements were performed. Adiponectin levels were measured using the "Linco Research" human adiponectin ELISA kit, and Leptin, TNF-α and IL-6 levels were measured using the "Biosource" human ELISA kit and the ELISA method simultaneously after thawing of the serum samples.

The SPSS (version 11.5) software package was used for the statistical analyses. Parametric and nonparametric methods were used for the analysis with a critical significance level of 0.05. The Mann-Whitney U test, Wilcoxon test and the independent samples test were used while accounting for whether the groups were independent or not. Correlation and regression analysis were also performed for the parameters.

Results

A total of 60 type I DM patients who consisted of 29 girls (48.3%) and 28 healthy children who consisted of 13 girls (46.4%) were included in this study. In the DM patient group, 29 (48.3%) had been diagnosed 5 or fewer years prior to the study, and 31 (51.7%) had been diagnosed more than 5 years prior to the study; 28 (46.7%) were in the prepubertal period, and 32 (53.3%) were in the pubertal period. The control group had 15 (53.6%) prepubertal and 13 (46.4%) pubertal children. There were no statistically significant differences in terms of age, weight, height, body mass index (BMI) and pubertal period between the patient and control groups (Table 1). The mean HbA1c level was 10.3±2.2% in the pubertal period type I diabetics and 9.1±1.8% in the prepubertal period type I diabetics (p=0.02). The triglyceride levels and the systolic and diastolic blood pressure were higher in the pubertal period study subjects compared to the prepubertal period subjects, whereas the HDL levels were lower.

The mean serum adiponectin level was 6.19±3.51 ng/dl in the type I diabetics and 5.00±1.82 ng/dl in the control group (p=0.042). There was no statistically significant difference in the serum leptin, TNF-α and IL-6 levels between the type I diabetic group and the control group. However, the serum leptin levels were higher in girls and during the pubertal period (Table 2).

Table 1. Mean age, weight, height and BMI values and comparisons between the patients and control groups

	Patients (n=60)	Control (n=28)	p value
Age (years)	12.7±3.4	11.8±2.1	0.16
Weight (kg)	45.4±15.2	37.2±11.9	0.27
Height (cm)	149.9±17.1	140.7±11.2	0.48
BMI (kg/m^2)	19.6±3.4	18.2±3.08	0.14

Table 2. Comparison between the adiponectin, leptin, TNF-α and IL-6 levels

	Patients (n=60)	Control (n=28)	p value	Male (n-44)	Female (n=44)	p value	Diagnosis of 5 years or less	Diagnosis of more than 5 years	p value	Prepubertal Period	Pubertal period	p value	Patients with microal buminuria (n=10)	Patients without microal buminuria (n=50)	p value	Patients with retinopathy (n=9)	Patients without retinopathy (n=51)	P value
Adiponectin (ng/dl)	6.19±3.51	5.00±1.82	0.042	6.1±3.1	5.5±3.2	0. 40	6.03±3.49	6.34±3.59	0.624	5.55±2.74	6.08±3.47	0.681	6.98±4.188	6.03±3.39	0.445	3.33±2.01	6.70±3.49	0.003
Leptin (ng/dl)	10.39±15.53	9.37±12.51	0.622	4.7±5.9	15.5±18.3	.001	7.71±9.65	13.07±19.56	0.472	5.32±4.75	14.61±18.85	0.016	21.30±19.18	8.21±13.92	0.041	26.95±30.07	7.47±9.05	0.007
TNF-α (pg/dl)	3.48±13.40	1.53±1.31	0.27	2.3±6.4	3.3±1.4	0.66	4.82±7.44	2.14±17.51	0.060	1.23±1.77	4.42±15.35	0.809	4.49±12.82	3.28±13.63	0.520	1.06±1.64	3.91±14.50	0.73
IL-6 (pg/dl)	12.39±9.68	11.67±9.68	0.741	12.1±10	12.2±9.3	0.93	12.56±9.65	12.11±9.18	0.379	11.68±8.87	12.62±10.37	0.650	11.89±8.95	12.14±10.07	0.306	13.15±4.64	12.25±10.36	0.158

Retinopathy was found in 9 (15%) of the 60 DM patients, and the mean diabetes duration of these patients was 9.61 (7-13) years; of these 9 patients, 7 (77.8%) were pubertal, and 2 (12.2%) were prepubertal. The glycemic control of these two prepubertal patients was impaired, and there was mild retinopathy (increased venous tortuosity was found on ophthalmological examination). The serum adiponectin levels were lower in the diabetic retinopathy patients (p=0.003), whereas the serum leptin levels were higher (p=0.007). There was no significant difference in the serum TNF-α and IL-6 levels between the patients with retinopathy and those without (Table 2).

Compared to the patients without diabetic retinopathy and microalbuminuria, patients with these complications showed higher serum leptin levels (p=0.001) and similar adiponectin, TNF-α, and IL-6 levels.

Adiponectin and leptin levels were negatively correlated with the presence of retinopathy, whereas leptin levels were positively correlated with female gender, age, weight, height, BMI, pubertal period, microalbuminuria, retinopathy, and systolic and diastolic blood pressure. TNF-α levels were positively correlated with urinary AER (r=0.288, p=0.026), whereas no correlation was found between the IL-6 levels and the measured parameters.

Linear regression analysis for adiponectin revealed regression between adiponectin and the presence of retinopathy only (p=0.008, r=0.34). Linear regression analysis for leptin showed regression for BMI (p<0.001, r=0.72), gender (p=0.004, r=0.76), presence of retinopathy (p=0.02, r =0.81), adiponectin (p=0.029, r=0.82) and insulin requirement (p=0.047, r=0.83).

Discussion

In this study, we found that serum adiponectin levels were increased in children and adolescents with type I DM. Similar results have been reported in the literature in type I DM [5-9], whereas type II DM has been associated with low serum adiponectin levels [10-13]. The increase in serum adiponectin levels in type I DM, in contrast to type II DM, may be due to a lack of insulin; glucose and insulin may play an important role in the increased serum adiponectin levels observed in type I DM [5, 14] However, Berg et al. showed that serum adiponectin levels do not change in mice after the onset of diabetes although the insulin levels decrease dramatically [15]. These findings indicate an indeterminate role for adiponectin in peripheral insulin sensitivity and regulation.

Despite studies that report lower adiponectin levels in men compared to women, during puberty compared to the prepubertal period and in association with obesity, insulin resistance and atherosclerosis [10, 16-18], we did not find any difference in adiponectin levels between males and females or between puberty and the prepubertal period (p>0.05). We

think that this lack of group differences may have occurred because the prepubertal and early pubertal male children in the study may have had high androgen levels. Androgens, such as testosterone and 5 α-hydroxy-testosterone are known to increase plasma adiponectin levels [14].

Studies on DM duration have also not found a relationship between the type I DM duration and serum adiponectin levels [5, 16]. However, Lindstrom found that the serum adiponectin levels were increased in patients with a diagnosis of type 1 DM for more than 10 years and stated that this may be due to the disturbed kidney functions related to the duration of DM [8]. Studies have also not found a relationship between metabolic control and the adiponectin levels [19].

There was an elevation in serum adiponectin levels with no statistical significance in the microalbuminuria patients ($p>0.05$). Several studies have reported that the adiponectin levels increase with the degree of microalbuminuria [6, 18, 20, 21].

Low serum adiponectin levels have been reported to be associated with increased retinopathy in type II DM [11, 22, 23]. However, Kato et al. recently described increased adiponectin levels in type II diabetic patients with retinopathy [24]. Based on their studies in type I diabetic patients, Hadjadj et al. reported that serum adiponectin levels were higher in patients with diabetic retinopathy [6]. In contrast, we found lower serum adiponectin levels in patients with diabetic retinopathy ($p=0.003$). This is the first study to show lower serum adiponectin levels in type I DM with retinopathy; however, to draw solid conclusions, these findings must be confirmed in larger series.

It has been shown that low grade inflammation plays a role in diabetic microangiopathy and that IL-6 has an important role in this inflammatory process [25, 26]. The anti-inflammatory effects of adiponectin include suppression of macrophage TNF-α secretion and inhibition of macrophage transformation into foam cells; in addition, a correlation between adiponectin and IL-6 has been found. However, Hadjadj et al. were unable to demonstrate a relationship between adiponectin and IL-6 [6]. We also did not find a correlation between adiponectin and TNF-α or IL-6 levels. Although many studies have described a role of TNF-α and IL-6 in insulin resistance, disturbed glucose tolerance and microangiopathy [9, 25-29), we were also unable to show such a relationship in our patients who had developed complications.

Similar to our findings, studies have shown that serum leptin levels increase with BMI, female sex, puberty and diabetic nephropathy but do not differ between type I DM patients and healthy controls [16, 30-33]. The serum leptin levels were found to be increased in patients with diabetic retinopathy compared to those without retinopathy ($p=0.007$). Similarly, serum and vitreous leptin levels were higher in type 1 and type 2 diabetic patients with diabetic retinopathy, and it was concluded that leptin played an important role in this diabetic complication [23, 34, 35].

We found higher serum adiponectin levels in children and adolescents with type I diabetes in this study but low levels in patients with diabetic retinopathy. The leptin levels were high in patients with diabetic retinopathy and microalbuminuria. In conclusion, we think that low serum adiponectin levels and high serum leptin levels are useful markers of diabetic retinopathy in children and adolescents.

Conflict of interest statement: The authors declare that they have no conflict of interest to the publication of this article.

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