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Leptin and Lipid Profile in Overweight Patient with Type 1 Diabetes

Soha M. Abd El Dayem[1*], Mona Abd El Kader[2], Soheir Ibrahim[3], Enas Mokhtar[1], Eman Abd El Megeed[4]

[1]Pediatrics Department, National Research Centre, Cairo, Egypt; [2]Clinical Pathology Department, National Research Centre, Cairo, Egypt; [3]Pediatrics Department, Al-Azhar University, Cairo, Egypt; [4]Pediatrics Department, Cairo, Egypt

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***Correspondence:** Soha Abd El Dayem. Professor of Pediatrics, Consultant of Diabetes and Endocrinology, Medical Research Division, National Research Centre, Pediatrics Department, Cairo, Egypt. Phone: +2 01006716852. E-mail: S_eldayem@yahoo.com

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Abstract

AIM: To evaluate leptin and lipid profile in overweight patients with type 1 diabetes.

PATIENTS AND METHODS: The study included 50 overweight patients with type 1 diabetes and 50 age and sex matched healthy controls. Blood samples were taken for evaluation of glycosylated haemoglobin, lipid profile and leptin. Also, urine samples were taken for evaluation of albumin/creatinine ratio.

RESULTS: Leptin level was significantly lower in overweight with type 1 diabetes and showed a significant positive correlation with hip circumference and body mass index and negative correlation with glycosylated haemoglobin (HbA1c). Leptin level was significantly lower in overweight diabetic patients with HbA1c > 7.5 %. The best cut-off point between overweight diabetic group and control group regarding leptin levels was found at 16.9 (ng/ml) with a sensitivity of 68% and specificity of 56%, area under the curve 0.623.

CONCLUSION: Leptin levels were found to be low in overweight patients with type 1 diabetes and showed correlation with the body mass index and hip circumference. LDL was significantly higher while HDL was significantly lower in the diabetic, overweight group indicating increased risk of cardiovascular disease. Leptin level in overweight diabetic patients might be related to the metabolic control.

Introduction

The incidence of type 1 diabetes is increasing 3–5% per year worldwide, and this increase is not related to genetic factors. A parallel increase in childhood obesity has occurred, and as a result, it is thought that obesity may be contributing to the increasing incidence of type 1 diabetes [1]. Body mass index (BMI) measured as weight in kilogrammes divided by height in meters squared. Childhood obesity, as defined by the American. Medical Association expert committee reports two cut-off values of 85th and 95th percentiles for BMI-for-age, from 85th up to 95th percentile being defined as ‘‘overweight’’ and BMI-for-age at or above the 95th percentile, being defined as ‘‘obesity’’ [2].

Inflammation is a condition that is common to both obesity and types 1 diabetes, and systemic inflammation is associated with the development of micro and macro vascular complications among persons with type 1 diabetes. However, the role of obesity compared with hyperglycemia in the development of inflammation among children with type 1 diabetes is unclear [3].

Leptin is a metabolic protein produced by the adipose tissue and both leptin and leptin receptors reported to be decreased in individuals with type 1 diabetes [4]. Leptin control food intake via brain signalling of satiety and energy store and is paradoxically increased with obesity, obese individuals appearing to be resistant to the effects of leptin [5].

The aim of our study was to evaluate leptin and lipid profiles in overweight patients with type 1 diabetes.

Patients and Methods

A cross-sectional observational study was performed after obtaining approval from the Ethical Committee of the National Research Centre, Cairo, Egypt. Written informed consent was obtained from all patients, their parents and controls after a full discussion about the aim of the study.

Fifty overweight children with type 1 diabetes, from the Endocrine Unit in the National Research Centre and fifty overweight health children without type 1 diabetes with age and sex matched were included as a comparative group.

Inclusion criteria

Overweight children (3-18years) with type 1 diabetes were included.

Exclusion criteria

Children using glucose-or lipid-lowering drugs; children using corticosteroids or drugs acting on the central nervous system; children with suspected syndromes with type 1 diabetes as Down syndrome and type 2 diabetes (T2DM); and children with other endocrinal causes of overweight, such as hypothyroidism, hypogonadism and pituitary disorders were excluded from the study.

Results

The study included 50 overweight patients with type 1 diabetes (34 females and 16 males), mean age of 15.74 ± 3.98 yr (3.5 – 18 yr) and meant duration of diabetes 10.01 ± 3.64 yr. The comparison between anthropometric and laboratory data of overweight diabetic and control group are shown in Table 1.

Table 1: Comparison between anthropometric and laboratory data of overweight diabetic and control group

	Diabetic group		Control group		Independent t-test	
	Mean	SD	Mean	SD	t	p-value
Systolic (mmHg)	117.30	14.29	118.20	6.29	0.408	0.685
Diastolic (mmHg)	75.50	10.06	76.00	5.35	0.310	0.757
Weight (kg)	67.62	12.05	57.78	9.71	-4.497	**0.000**
Height (cm)	158.67	11.31	158.43	14.97	-0.089	0.929
Waist (circumference)	85.49	9.39	75.73	8.29	5.436	**0.0001**
Hip (circumference)	94.84	8.52	91.21	9.08	-2.052	**0.043**
Waist/hip (ratio)	0.90	0.06	0.83	0.08	4.665	**0.0001**
Waist/height (ratio)	0.54	0.06	0.48	0.05	5.150	**0.0001**
BMI (kg/ m^2)	27.03	1.78	27.55	1.49	1.582	0.117
Cholesterol (mg/dl)	180.92±44.47	107 – 287	173.24±33.96	113 – 287	-0.964	0.338
Triglyceride (mg/dl)	97.32±48.11	29 – 288	91.76 ± 32	45 – 160	-0.676	0.501
HDL-c (mg/dl)	51.80±25.38	20 – 180	65.48 ± 22.4	50 – 180	2.813	**0.006**
LDL-c (mg/dl)	108.83±33.85	51 – 197	80.49 ± 23.41	25 – 100	-4.599	**0.0001**

BMI: Body mass index; Bold indicates significant.

Leptin levels were significantly lower in the group of overweight diabetic patients (Table 2).

Table 2: Comparison between overweight diabetic control group regarding serum leptin level

	Diabetic group	Control group	Mann-Whitney test	
	Median (IQR)	Median (IQR)	Z	P-value
Leptin (ng/ml)	11 (5.2 - 24.8)	18.3 (9.9 - 32.6)	2.127	**0.033**

Boldly indicates significant.

Leptin levels showed significant positive correlation with hip circumference and body mass index and negative correlation with HbA1c in overweight diabetic patients (Table 3).

Table 3: Correlation between leptin and demographic, anthropometric and laboratory data of overweight diabetic group

	Leptin	
	N	p-value
Age (yrs)	0.066	0.648
Duration of disease (yrs)	0.100	0.488
Onset of disease (yrs)	-0.029	0.841
Insulin (U/kg)	0.011	0.944
Systolic blood pressure (mmHg)	-0.210	0.142
Diastolic blood pressure (mmHg)	-0.146	0.31
Weight (kg)	0.044	0.762
Height (cm)	0.004	0.98
Waist circumference	0.148	0.311
Hip circumference	0.320	**0.025**
Waist/hip ratio	-0.170	0.096
Waist/height ratio	-0.053	0.609
BMI (kg/m^2)	0.286	**0.044**
HbA1c (%)	-0.665	**0.0001**
Albumin/ creatinine ratio (µg/g creatinine)	-0.015	0.916
Cholesterol (mg/dl)	0.015	0.919
Triglyceride (mg/dl)	-0.035	0.811
HDL-c (mg/dl)	-0.051	0.728
LDL-c (mg/dl)	0.112	0.461

BMI: Body mass index, HbA1c: glycosylated hemoglobin, HDL-c : high density lipoprotein cholesterol, LDL-c: Low density lipoprotein cholesterol. Bold indicates significant.

Leptin level was significantly lower in overweight diabetic patients with HbA1c > 7.5 % (Table 4).

Table 4: Comparison between leptin levels in overweight diabetic group regarding HbA1c

	N	Leptin level Median (IQR)	Mann-Whitney test Z	p-value
HbA1c < 7.5 %	11	30.7 (8.2 – 39.1)	2.513	**0.011**
HbA1c > 7.5 %	39	11.0 (5.1 – 17.7)		

Boldly indicates significant.

There was a significant positive correlation between leptin and body mass index of the control group as shown in Table 5.

The correlation between lipid parameters and other demographic data in the overweight diabetic group are given in Table 6.

The best cut-off point between overweight diabetic group and control group regarding the level of leptin was found 16.9 ng/ml with a sensitivity of 68% and specificity of 56% and area under the curve of 0.623.

Table 5: Correlation between leptin, and demographic, anthropometric and laboratory data in the overweight control group

	Leptin	
	N	p-value
Age (yrs)	0.010	0.947
Weight (kg)	0.010	0.945
Height (cm)	-0.029	0.843
Systolic (mmHg)	0.050	0.728
Diastolic (mmHg)	0.004	0.979
Waist (circumference)	-0.223	0.120
Hip (circumference)	-0.157	0.277
BMI (kg/m^2)	0.294	**0.038**
Waist/hip ratio	-0.091	0.528
Waist/height ratio	-0.122	0.398
Cholesterol (mg/dl)	0.050	0.733
Triglyceride (mg/dl)	-0.014	0.923
HDL-c (mg/dl)	-0.096	0.517
LDL-c (mg/dl)	0.071	0.648

BMI: Body mass index, HbA1c: glycosylated hemoglobin, HDL-c: high density lipoprotein cholesterol, LDL-c: Low density lipoprotein cholesterol. Bold indicates significant.

Discussion

In the present study, we found that the median (IQR) serum leptin level was significantly lower in the diabetic, overweight group 11 (5.2 - 24.8) ng/ml compared to the non-diabetic, overweight group 18.3 (9.9 - 32.6) ng/ml. It was consistent with the findings of Kirel et al., [12], Abd EL- Maksoud et al., [13] and Kratzsch et al., [14], who stated that decompensation of metabolism in children with newly diagnosed type 1 diabetes is associated with changes in the leptin axis, with elevated soluble leptin receptors and reduced leptin levels.

Table 6: Correlation between lipid profile and other demographic data in overweight diabetic group

	Cholesterol		Triglyceride		HDL-c		LDL-c	
	r	P-value	r	P-value	r	P-value	r	P-value
Age (yrs)	0.006	0.968	-0.172	0.233	0.139	0.339	-0.068	0.642
Duration of disease (yrs)	-0.054	0.712	0.014	0.924	-0.192	0.187	0.076	0.602
Onset of disease (yrs)	0.036	0.801	-0.084	0.560	0.229	0.113	-0.170	0.244
Inslulin dose (U/Kg)	-0.007	0.967	0.072	0.650	-0.179	0.263	-0.026	0.871
Systolic blood pressure (mmHg)	0.052	0.720	0.158	0.274	0.035	0.811	-0.027	0.854
Diastolic blood pressure (mmHg)	-0.028	0.846	0.078	0.591	-0.301	**0.036**	0.020	0.893
Weight (kg)	-0.056	0.699	0.070	0.631	-0.278	**0.053**	0.106	0.470
Height (cm)	-0.132	0.360	-0.021	0.884	-0.438	**0.002**	0.132	0.368
Waist circumference (cm)	0.081	0.578	0.059	0.688	-0.097	0.511	0.219	0.134
Hip circumference (cm)	-0.029	0.845	-0.072	0.621	-0.223	0.127	0.195	0.185
BMI (kg/m^2)	0.058	0.688	0.121	0.403	0.024	0.870	0.234	0.105
HbA1c (%)	0.214	0.139	0.170	0.242	0.073	0.620	0.270	0.063

BMI: Body mass index, HbA1: glycosylated hemoglobin, HDL-c: high density lipoprotein cholesterol, LDL-c: Low density lipoprotein cholesterol. Bold indicates significant.

The molar excess of soluble leptin receptors over leptin in this condition may contribute to leptin insensitivity. Also, the diminished leptin concentrations in patients with newly diagnosed type 1 diabetes could be caused by insulin deficiency and increased lipolysis [15].

Soliman et al., [16] and Snell-Bergeon et al., [17] suggested that leptin is lower in newly diagnosed patients with type 1 diabetes than in children with longer disease duration, perhaps related to differences in peripheral insulin levels and fat mass.

Table 7: Receiver operating characteristic curve for the cut-off point of leptin between the overweight diabetic group and control group

Cut off point	AUC	Sensitivity	Specificity	PPV	NPV
≤16.9 ng/ml	0.623	68.00	56.00	60.7	63.6

AUC: Area under the curve, PPV: Positive predictive value, NPV: Negative predictive value.

In the present study, we reported that there was a statistically significant positive correlation between the mean serum leptin levels and BMI in the diabetic, overweight group and the non-diabetic, overweight group and this was by Al Maskari et al., [18] and Abd EL-Maksoud et al., [13]. Nishimura et al., [19] also revealed that serum leptin levels in school children aged from 9-13 years were positively correlated with the body mass index, irrespective of age or gender. Another study by Antunes et al., [20] of overweight children with mean age of 9.5 years showed that BMI and gender were determinant.factors of leptin levels [21].

Type 1 diabetics have a high risk of cardiovascular disease (CVD), and premature atherosclerosis represents the main cause of morbidity and mortality in diabetic populations [22]. Many types of research revealed that atherosclerosis begins early in life and therefore, determination and preventive strategies of risk factors for CVD should be started during childhood and adolescence [23]. Type 1 diabetic children and adolescents are a high-risk population with regards to CVD, given that cardiovascular risk factors are common among them [23-25] leading to poor long-term prognosis [26]. It has been shown that as many as 86% of youth with type 1 diabetes have at least one, 45% at least two and 15% at least three CVD risk factors, including high HbA1c, high blood pressure, dyslipidemia, smoking and family history of CVD events [24]. High incidence of dyslipidemia has often been reported in patients with type1 diabetes up to 58% of type 1 diabetics were found to be hyperlipidemic [27, 28].

In the present study, we found that the HDL was statistically significantly lower and LDL was significantly higher in the diabetic, overweight group. Also, triglycerides and total cholesterol levels were high in the diabetic, overweight group.

Salem et al., [29] conducted a study on type 1 diabetic patients with mean age of 15.93 ± 1.99 years and showed that dyslipidemia was prevalent in those patients where triglycerides, total cholesterol and LDL cholesterol were significantly higher while HDL cholesterol was decreased compared with controls. Therefore, we should evaluate lipids soon after diagnosis in type 1 diabetic children aged more than 12 years, and it should be repeated every five years if normal results are obtained. Statins should be started

if interventions to improve metabolic control and dietary changes could not help to reach the target level [30].

This finding is in agreement with Gunczler et al., [31] who found that TC, LDL-C and Tg levels were elevated in 34.4%, 25.0% and 15.6% of the adolescents with type 1 diabetes respectively compared with 20.0%, 13.3% and 6.7% of the control subjects.

Snell-Bergeon et al., [17] reported an increase in total and LDL-cholesterol as well as increased apo B. Also, higher levels of IL-6 were associated with lower levels of HDL-cholesterol. These results showed that systemic inflammation is high in type 1 diabetics, irrespective to hyperglycemia and obesity and it is associated with a more atherogenic lipid profile, putting these youth at higher risk of cardiovascular disease.

Hassan et al., [32] found that the most frequent type of dyslipidemia was high LDL-C and low HDL-C in 28.2% of the children and adolescents with type 1 diabetes and dyslipidemia, while high LDL-C and hypercholesterolemia with and without hypertriglyceridemia were found to be the most common types in Al-Naama et al., [33] and Rahma et al., [34]. The diabetic children in the previous two studies showed poor high-risk glycemic control according to the mean fasting blood glucose (FBG) (232.0 ± 92.0 mg/dl) and HbA1c (9.8 ± 4.2%) levels.

Herman et al., [35] and Kantoosh et al., [36] reported that in Egyptian diabetic children, hypertriglyceridemia was the predominant type and reported significantly higher serum Tg and HbA1c levels in the untreated newly diagnosed children with type 1 diabetes in comparison to the treated diabetics with good glycemic control. Patiakas et al., [37] found that hypercholesterolemia was the most frequent type, and hypertriglyceridemia is the least frequent type in diabetic patients in contrast to Already et al., [38] who reported that high triglyceride is a common pattern of dyslipidemia in type 1 diabetics children and adolescents.and it is related to different levels of glycemic controls.

In the present work, no significant correlation was found between the duration of disease and lipid abnormalities in the diabetic, overweight group. This finding in agreement with Maahs et al., [39] who found that there was no relationship between the lipid abnormalities in paediatric type 1 diabetes and the duration of diabetes.

Hamad and Qureshi [40], Guy et al., [41] and Kanagalakshmi and Sultana (42) found that dyslipidemia in children and adolescents with type 1 diabetes is present despite the short duration of diabetes. This is in contrast to the results reported by Moayeri and Oloomi [43] who found that lipid concentrations correlate positively with the duration of diabetes. Also, Schwab et al., [44] stated that atherogenic risk factors as dyslipidemia in children and adolescents with type 1 diabetes are related to the longer duration of diabetes.

In our study, there was no statistical difference in the mean age, gender and the lipid abnormalities. This finding in agreement with Alrabaty et al., [38] and Patiakas et al., [37]. They reported that there was no relationship between gender and lipid abnormalities in type 1 diabetic children and adolescents. Also Ladeia et al., [45], Maahs et al., [39] and Wiltshire et al., [46], found no significant correlation between age and serum LDL-C of the patients with diabetes.

This finding is in contrast to the results reported by Krantz et al., [47] and Schwab et al., [44] who found that lipid levels were significantly higher in female subjects compared with male subjects with type 1 diabetes. However, no significant difference of HDL-C was found between female and male subjects by Schwab et al., [44]. Moayeri and Oloomi [43] found that the higher mean age of children and adolescents with T1DM is associated with more frequent dyslipidemia.

In our study, we found that there was statistically significant lower median leptin level in the diabetic, overweight subgroup with HbA1c > 7.5. Our findings were consistent with a study done by Snell-Bergeon et al., [17] and Abd El- Maksoud et al., [13], who showed that the leptin levels were lowest among patients with higher HbA1c.

Al-Suhaimi et al., [48] stated that there was a positive significant correlation of leptin with HbA1c. However, they explained this correlation by the finding of Soliman et al., [16] who reported that over substitution by insulin exerted many metabolic actions contributing to the elevation of leptin release. They attributed the higher leptin levels glycemic control to type 1 children with diabetes (higher circulating HbA1c concentrations that those treated with insulin).

Regarding mean HbA1c values, we observed no significant correlations between HbA1c and serum TC, TG and LDL-C; this result is in concordance with Muchacka-Bianga et al., [49] and Kantoosh et al., [36] who found that lipid disorders in children with T1DM may be present regardless of their metabolic control. On the contrary, Teles and Fornés [50] and Guy et al., [41] found that poorer (inadequate) glycemic control is related to higher serum lipids levels. Ladeia et al., [45] and Krantz et al., [47] found significant correlations between glycemic control and lipid levels.

In our study, ROC curve analysis revealed that the cutoff point between the diabetic, overweight group and non-diabetic, overweight group regarding the level of leptin was found at 16.9 ng/ml with a sensitivity of 68% and specificity of 56%. Type 1 diabetic patients with levels above this cut-off may have a higher risk of developing complications and should be closely followed up. However, to the best of

our knowledge, no previous studies assessed leptin cut off in type 1 diabetes and therefore, further prospective studies are needed to validate these thresholds.

In conclusion, low leptin levels were observed in overweight diabetic patients and were shown to be correlated to body mass index and hip circumference. LDL was statistically significantly higher while HDL was significantly lower in the diabetic, overweight group indicating increased risk of cardiovascular disease. Leptin level in overweight diabetic patients may be related to metabolic control.

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