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Association between Serum Adiponectin and Insulin Resistance in Children and Adolescents with Type 1 Diabetes: A Cross-Sectional, Single Center Study from Egypt

ABSTRACT

Objective: To determine the serum level of adiponectin and its relation to insulin resistance (IR) in children and adolescents with type 1 diabetes (T1D).

Materials and methods: Over a 3-month period, 65 children diagnosed with T1D who were followed up at the Diabetes Endocrine and Metabolism Pediatric Unit (DEMPU) at Cairo University Children's Hospital. Demographics, clinical data, investigations, and management details were collected from the patient's medical records and evaluated for the serum level of adiponectin.

Results: Mean age of the study population was 12.6 ± ± 2 years. About 40% of participants had low serum adiponectin, with a mean value of 2.4 ± 3.6. Sixty-one (93.8%) of participants had dyslipidemia. The mean estimated glucose disposal rate (eGDR) was 6.9 ± ± 2.1. Multivariate linear regression was performed to adjust for possible confounders in correlation between serum adiponectin and eGDR; it wasn't significant as p-value = 0.875. There was a statistically significant difference between patients with normal and low adiponectin regarding the age of diagnosis of diabetes, body mass index, the occurrence of microalbuminuria, and LDL level, with p-values of 0.04, 0.015, 0.022, and 0.011, respectively.

Conclusions: There was also an association between lower adiponectin levels in children with type 1 diabetes and the occurrence of microalbuminuria and dyslipidemia. However, there is no reported association between its level and IR. (Clin Diabetol 2023; 12; 3: 150–155)

Keywords: adiponectin, insulin resistance, dyslipidemia, type 1 diabetes

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Introduction

Type 1 diabetes (T1D) is a complex childhood chronic autoimmune condition that gradually destroys insulin-producing pancreatic islet cells through an autoimmune mechanism [1]. The incidence of T1D increases in many countries, especially among children and adolescents below 15 years [2]. Egypt contributes significantly to the estimated T1D childhood cases in the Middle East and Eastern Mediterranean countries, which accounts for about 25%. In Egypt, the incidence

varies between 8/100,000 per year in children younger than 15 years [3].

There is a rising trend of overweight and obesity among individuals with T1D. This is often associated with insulin resistance (IR), suboptimal glycemic control in T1D, increased insulin dose requirements and poor glycemic control. IR is also seen during puberty and is strongly related to increased risk of cardiovascular disease [4].

Insulin sensitivity testing techniques require precise insulin measurement. Insulin tests have evolved and exhibited significant interlaboratory variability [5]. The hyper-insulinemic euglycemic clamp provides a direct measure of insulin-stimulated glucose disposal (mainly by the muscle). Its main drawback is that it takes a long time to set up (at least 2–3 hours per patient), and trained operators must be present to control the infusions, draw blood, monitor blood glucose every 5 minutes, and alter glucose infusion rates [6].

There are different methods to evaluate IR, such as measurement of fasting plasma insulin (FPI), the homeostasis model assessment of insulin resistance (HOMA-IR), and the quantitative insulin sensitivity check index (QUICKI). Nevertheless, they cannot be used in assessing IR in T1D.

In patients with T1D, the estimated glucose disposal rate (eGDR) has been proven to be a key indicator of IR, with decreased eGDR levels suggesting IR [7].

White adipose tissue is a primary energy storage location, essential for maintaining energy balance. It has become a well-known critical endocrine tissue that releases biologically active adipokines, such as adiponectin [8].

Adiponectin plasma concentration is lowered in human obesity, particularly visceral obesity. As reported in many studies, it is adversely associated with IR [9]. Hypoadiponectinemia can cause endothelial dysfunction by decreasing insulin sensitivity. The significant associations of adiponectin levels with clinical and cardiometabolic parameters reveal its potential as a biomarker in assessment of prediabetic state and T2D screening [10]. However, few studies were done to assess the relationship between serum adiponectin and IR in children and adolescents with T1D. Our main aim was to detect if serum level of adiponectin can be used as an appropriate marker to measure IR in children and adolescents with T1D. This could help to counter IR, avoiding macrovascular complications among these individuals.

Materials and methods

Study design

This cross-sectional study included 65 children diagnosed with T1D who were followed up at the Diabetes Endocrine and Metabolism Pediatric Unit (DEMPU) at Cairo University Children's Hospital over 3 months from November 2020 to January 2021.

Study population

Children aged 10–18 years, with diabetes duration more than 2 years were recruited. Children with other associated autoimmune diseases, those receiving drugs that alter insulin sensitivity as Metformin were excluded. The DEMPU records were revised, and data were collected, including age, sex, initial presentation [diabetic ketoacidosis (DKA) or hyperglycemia], whether the patient was newly diagnosed or known to have T1D, duration of diabetes, a daily dose of insulin (U/kg/day), family history of diabetes (T1 or T2), hypertension, and dyslipidemia. They were subjected to clinical assessments, including anthropometric measurements – weight (SD), height (SD), BMI (SD), waist circumference (cm), hip circumference (cm), and waist-to-hip ratio. They were calculated using the Growth Vision program, version 2 provided by Novo Nordisk. The pubertal assessment was carried out using Tanner staging. Lipodystrophy was detected at the insulin injection sites, acanthosis nigricans represented a sign of IR, and limited joint mobility represented poor metabolic control. Blood pressure measurement (using mercury sphygmomanometer in 3 different occasions within 2 weeks). Measurements were classified according to percentiles into normal, prehypertension and hypertension.

Variables and measurements

Investigations were obtained from the patient's files, including glycated hemoglobin (HbA1c). HbA1c test reflects a time averaged blood glucose during the previous 2–3 months and is used as the gold standard for long-term follow-up [11]. HbA1c was determined by high performance liquid chromatography using the Bio-Rad hemoglobin testing system, D-10 Dual Program. The mean level was obtained all over the preceding year. A target of < 53 mmol/mol ($< 7.0\%$) is recommended for all young people with diabetes. Estimated glucose disposal rate (eGDR) is a validated clinical tool for estimating insulin sensitivity in type 1 diabetes [11]. It was reported to correlate to IR inversely; therefore, the lower the eGDR levels, the greater the IR [12]. It was calculated as follows:

$$\text{eGDR} = 24.31 - (12.22 \times \text{WHR}) - (3.29 \times \text{HT}) - \\ - (0.57 \times \text{HbA1c})$$

where WHR is the waist-hip ratio, HT is the hypertension history, and HbA1c represents glycated hemoglobin A1c [13].

eGDR level is classified as follows: normal (85–150 mL/ /min/1.73m^2) and low (< 85 mL/min/1.73m^2).

Lipid profiles were also obtained. The American Diabetes Association defined dyslipidemia as having LDL-C greater than 100 mg/dL, HDL-C less than 40 mg/dL (males) and less than 50 mg/dL (females), TC greater than 200 mg/dL, and TG greater than 150 mg/dL. Dyslipidemia was present if one or more lipid or lipoprotein levels were abnormal [14]. Microalbumin in urine: microalbuminuria (MA) was determined in a random spot collection using the immunoturbidimetric assay. Calculation of albumin/creatinine ratio was expressed in mg albumin/g creatinine. The diagnosis of MA was determined when the level exceeded 30 mg/gm creatinine, while macroalbuminuria was present when the level exceeded 300 mg/gm creatinine. Adiponectin is an adipokine secreted by adipocytes, is a well-known homeostatic factor for regulating glucose levels, lipid metabolism, and insulin sensitivity through its anti-inflammatory, anti-fibrotic, and antioxidant effects.

Assessment of serum adiponectin levels was carried out using the Human Adiponectin ELISA Kit; available ELISA kit (Cat No: SG-10784, sinoGeneClon Biotech Co., Ltd, HangZhou, China). The reference range was 0.5–32 ng/mL. The minimum detectable dose of adiponectin is typically 0.25 ng/mL.

Samples for adiponectin were centrifuged at a speed of 2000-3000 rpm for 15 min after leaving at room temperature for 10–20 min. The supernatant was removed and stored at –20°C till time of assay. Serum adiponectin was assayed using commercially available ELISA kit. The standard preparation supplied with the assay was used to plot standard curve. The optical density readings at 450 nm were converted to concentrations in ng/mL after the reaction.

The authors declare absence of conflict of interest and that they had complete access to data and information relevant to the study.

This study protocol was reviewed and approved by Research Ethics Committee (REC), Faculty of Medicine, Cairo University, approval number [MS-120-2020].

Statistical analysis

Data management and statistical analysis were performed using the Statistical Package for Social Sciences (SPSS) version 24.

Numerical data were summarized using means ± standard deviations, or medians and ranges. The data were explored for normality using the Kolmogorov-Smirnov and the Shapiro-Wilk tests. Categorical data were summarized as percentages. Comparisons between the two groups were made using the independent t-test. For categorical variables, differences were analyzed with the chi-squared test and Fisher's exact test when appropriate. A Pearson correlation coefficient was determined between serum (adiponectin) and different numeric variables. All p-values were two-sided. P-values ≤ 0.05 were significant.

Results

Over a 3-month period, 65 children had T1D with a male predominance (males 56.9%, females 43.1%), and a male to female ratio of 1.3:1. Their mean age was 12.6 ± 2 years old, the mean age of diagnosis was 7.3 ± 2.8 years old, and the mean diabetes duration was 5.4 ± 2.8 years. Demographic and clinical data of the study group are summarized in Table 1.

Twenty-six (40%) patients of the study group had low serum adiponectin with the mean value 2.4 ± 3.6. The mean value of estimated glucose disposal rate (eGDR) was 6.9 ± 2.1 with median 7.2 and range between (1.7–10.7). Fifty (76.9%) patients of the study group had low level of eGDR while 15 (23.1%) had normal level of eGDR.

Multivariate linear regression was used to study the relationship between serum adiponectin and eGDR that was used as an indicator of insulin resistance, by adjusting the age, sex and diabetes (diabetes duration, HbA1c, fasting and 2-hour postprandial blood glucose, DKA). It showed no statistical significance with a P value of 0.875, as illustrated in Table 2.

Most children (82.4%) in the present study were poorly controlled as the mean HbA1c was 9.6 ± 1.5.

The mean systolic BP among study group was 104.6 ± 11.7 mmHg, 40% of the study group were hypertensive, the mean diastolic BP was 73.7 ± 8.9 mmHg, 52.3% of the study group were prehypertensive, and the mean of mean arterial pressure (MAP) was 84.1 ± 8.7. About 40% of the study group were pubertal. All the study group showed no signs of lipodystrophy, and only 16.9% had signs of poor metabolic control in the form of limited joint mobility.

Sixty-one (93.8%) patients had dyslipidemia, with a mean LDL of 134.4 ± 40.9 mg/dL, HDL of 50.1 ± ± 14 mg/dL, TG of 110.6 ± 31.9 mg/dL, and total cholesterol of 157.9 ± 39.4 mg/dL.

By comparing patients with normal and low serum adiponectin levels, there was a statistically significant difference in the age of the diagnosis of diabetes, with a p-value of 0.04. In addition, a statistically significant difference was found between the two groups regarding BMI (SD), LDL, and microalbuminuria, with p-values of 0.015, 0.011, and 0.022 respectively. Patients with low adiponectin levels had higher BMI, LDL, and microalbuminuria than those with normal adiponectin levels as shown in Table 1. Coefficient of variation (CV) of

Table 1. Demographic, Anthropometric, and Clinical Data of the Study Group (n = 65) and Comparison between Patients with Normal and Low Adiponectin

	Overall group (n = 65)	Normal adiponectin	Low adiponectin
Age [years] mean ± SD	12.6 ± 2	12.4 ± 2.0	13.0 ± 1.9
Sex: female (F), male (M)	F: 28 (43.1%)	17 (60.7)	11 (39.3)
	M: 37 (56.9%)	22 (59.5)	15 (40.5)
Age of diagnosis of diabetes [years] mean ± SD	7.3 ± 2.8	6.8 ± 2.7	8.2 ± 2.8
Duration of diabetes [years] mean ± SD	5.4 ± 2.8	5.9 ± 2.9	4.8 ± 2.5
Daily dose [U/kg/day] mean ± SD	1.4 ± 0.3	1.4 ± 0.3	1.4 ± 0.3
Weight SD mean ± SD	–0.7 ± 1.1	–0.8 ± 1.1	–0.4 ± 1.1
Height SD mean ± SD	–1.4 ± 1.2	–1.4 ± 1.2	–1.5 ± 1.2
BMI SD mean ± SD	0.1 ± 1.3	–0.3 ± 1.4	0.5 ± 0.8
Waist circumference [cm] mean ± SD	70.6 ± 9.5	68.9 ± 8.0	73.2 ± 11.1
Hip circumference [cm] mean ± SD	82.9 ± 10.3	81.9 ± 9.5	84.3 ± 11.5
WHR mean ± SD	0.9 ± 0.1	0.8 ± 0.1	0.9 ± 0.0
Mean arterial pressure (MAP) mean ± SD	84.1 ± 8.7	85.7 ± 7.4	81.8 ± 10.0
Manifestations (polyuria, polydipsia, polyphagia, loss of weight)	47 (72.3%)	25 (53.2)	22 (46.8)
DKA	18 (27.7%)	14 (77.8)	4 (22.2)
Family history of diabetes	35 (53.8%)	23 (65.7)	12 (34.3)
Family history of dyslipidemia	10 (15.4%)	9 (90.0)	1 (10.0)
Family history of hypertension	12 (18.5%)	7 (58.3)	5 (41.7)
HbA1c mean ± SD	9.6 ± 1.5	9.7 ± 1.4	9.5 ± 1.5
eGDR mean ± SD	6.9 ± 2.1	7.1 ± 2.0	6.6 ± 2.1
Microalbuminuria in urine mean ± SD	16.1 ± 8.9	14.0 ± 6.9	19.2 ± 10.7
LDL mean ± SD	134.4 ± 40.9	123.9 ± 38.2	150.0 ± 40.6

BMI — body mass index; DKA — diabetic ketoacidosis; eGDR — estimated glucose disposal rate; LDL — low-density lipoprotein; SD — standard deviation; WHR — waist-to-hip ratio

Table 2. Multivariate Linear Regression to Adjust for Possible Confounder in Correlation between Serum Adiponectin and eGDR

	P-value
eGDR	
Age [years]	0.157
Sex	0.852
Duration of T1D	0.113
Age of diagnosis of T1D	0.108
DKA	0.891
HbA1c	0.044
FBG	0.113
2hPPBG	0.290
Serum adiponectin	0.875

2hPPBG — 2-hours postprandial blood glucose; DKA — diabetic ketoacidosis; eGDR — estimated glucose disposal rate; FBG — fasting blood glucose; HbA1c — glycated hemoglobin; T1D — type 1 diabetes

HbA1c, microalbumin, adiponectin was 15.6%,55.3%, 150% respectively.

Discussion and conclusions

Insulin resistance is more frequently observed among adolescents with T1D compared to children due to a rise in sex steroids during puberty that antagonize insulin action and contribute to the development of IR.

According to a previous study, adiponectin plasma concentration was lowered in humans with obesity, particularly visceral obesity, and was adversely associated with IR [9]. Moreover, hypoadiponectinemia was associated with metabolic syndrome (MS) as an indicator of IR [15].

In the current study, most of children with T1D had IR that was measured by eGDR. This was consistent with the studies conducted by Soliman et al. [16] and Saki et al. [17], who studied the prevalence and clinical profile of metabolic syndrome (MS) among children with T1D. They concluded that eGDR was significantly lower in the MS group indicating significantly higher IR in patients with T1D who developed MS.

Regarding the current marker, 40% of the study group had low serum adiponectin, with a statistically significant difference between those with low and

normal adiponectin levels regarding the age of diabetes because patients diagnosed at an older age had lower adiponectin levels than patients diagnosed at a younger age. This agreed with the study by Lecaire et al. (2015) [18], which revealed that the mean value of adiponectin in T1D children was 11.9 mg/dL after one year of examination and 10.2 mg/dL after 20 years of examination, which showed a decline in adiponectin level throughout diabetes. Serum adiponectin was inversely correlated to eGDR by adjusting other confounders as age, sex, diabetes duration, HbA1c, attacks of DKA. This contrasts with the study done by Blaslov et al. (2013) [15] who studied the relationship between adiponectin level, insulin sensitivity, and metabolic syndrome in adult patients with T1D. They found that patients with higher plasma adiponectin showed higher eGDR levels indicating higher insulin sensitivity.

Nevertheless, there was no statistically significant difference between patients with normal and low adiponectin levels regarding their glycemic control. This finding was inconsistent with what was reported in the study by Karamifar et al. (2013) [20], who mentioned that T1D children with low adiponectin levels had poor metabolic control, while those with normal adiponectin had reasonable metabolic control.

In the present study, patients with higher BMI had lower adiponectin levels, while those with lower BMI had normal adiponectin levels. This agreed with the study by Kishida et al. (2011) [19] who found a significant relationship between serum adiponectin levels and BMI in T1D patients. Nevertheless, this revealed that fat reservation was essential for serum adiponectin levels. Since low adiponectin levels led to a slow rate of fatty acid oxidation, higher amounts of fatty acids led to IR [20].

The present study showed a statistically significant negative correlation between serum adiponectin and LDL levels. This showed that children with type 1 diabetes with low adiponectin levels had higher LDL levels than those with normal adiponectin, consistent with Izadi et al. (2013) [21], who found a statistically negative correlation between serum adiponectin levels and LDL. It also emphasized the role of adiponectin in the metabolism of lipid profiles.

This was inconsistent with the study conducted by Blaslov et al. (2013) [15], which found no statistically significant correlation between serum adiponectin and LDL.

In this study, there was a statistically significant difference between patients with normal and low adiponectin levels regarding the occurrence of microalbuminuria. Patients with lower adiponectin levels had microalbuminuria than those with normal adiponectin levels. This was inconsistent with the study by Al Saeed et al. (2014) [22], who evaluated serum adiponectin levels in T1D children and their relation to diabetic complications. They reported a significant increase in adiponectin levels in T1D patients who developed microalbuminuria.

Previous studies with adolescents and children revealed a significant association between adiponectin and markers of IR, such as fasting serum insulin or homeostasis model assessment of insulin resistance (HOMA-IR) [23].

Kowalska et al. (2008) [23] found that declines in adiponectin concentrations and rises in fasting insulin were more significant in people who met a higher number of metabolic syndrome criteria according to the National Cholesterol Education Program Criteria.

The current study's limitations were that it was a cross-sectional and clinic-based study. It is not a multicenter or population-based study. Diverse age and diabetes duration with suboptimal diabetes control. More longitudinal studies focused on children needed to be done that spanned the time range from childhood diabetes diagnosis to long-term diabetes in adulthood.

It is concluded from the current study that serum adiponectin levels may decrease in children with T1D, but there is no reported association between its levels and IR that was measured by eGDR. However, there is an association between lower adiponectin levels in children with type 1 diabetes, dyslipidemia, and the occurrence of microalbuminuria. Further studies are required because little is known about how adiponectin levels change over time in children with T1D and whether factors related to adiponectin levels differ between early and late diabetes.

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Conflict of interests

None declared.

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