

## Adiponectin as a Marker of Complications in Type I Diabetes

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**Objective:** To evaluate adiponectin levels in children and adolescents with type I diabetes, and their relationship to long term complications.

**Design:** Cross sectional.

**Setting:** Tertiary referral hospital, Cairo, Egypt.

**Participants:** Thirty children and adolescents with type I diabetes mellitus, classified into complicated and non-complicated and compared to 10 healthy age and sex matched subjects as a control group.

**Methods:** All children underwent anthropometric measurements, neurological assessment, fundus examination, echocardiography and assays of HbA<sub>1c</sub>, creatinine, 24-hr urinary protein, and serum

adiponectin.

**Main outcome measure:** Relationship of serum adiponectin to complications of type I diabetes mellitus, and glucose control.

**Results:** Serum adiponectin was significantly elevated in complicated diabetes (10.3±5.9 pg/dL) as compared to the controls (6.5±3.7pg/dL) ( $P<0.01$ ), and correlated directly with HbA<sub>1c</sub> ( $P<0.05$ ) and creatinine ( $P<0.001$ ). Patients with nephropathy showed high values of adiponectin (15.7±3.7 pg/dL).

**Conclusion:** Elevated adiponectin level in children and adolescents with type I diabetes indicates poor glycemic control and development of complications, especially nephropathy.

**Key words:** Adiponectin, Complications, Diabetes, Prognosis.

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Type I diabetes mellitus is characterized by marked inability of the pancreas to secrete insulin [1]. The morbidity and mortality associated with diabetes is related to its short and long term complications [2]. Adiponectin is a protein hormone that modulates a number of metabolic processes. Levels of the hormone are inversely correlated with body mass index (BMI) [3]. In adults, lower circulating levels of the adipocyte-derived hormone are associated with obesity, type 2 diabetes and microvascular disease risks. In type I diabetic patients, the relationship between adiponectin and the presence of vascular complications is largely unknown [4]. Further, its use as a risk marker in children is less clear [5].

We conducted this study to evaluate the levels of adiponectin in children and adolescents with type I diabetes, and its possible relationship to the occurrence of complications.

### METHODS

This cross sectional study, comprised 30 children and adolescents recruited consecutively from Children's hospital, Ain Shams University. They were diagnosed

with type I diabetes according to the American Diabetes Association criteria [6]. Based on the results of the evaluation, they were classified into complicated group (with one or more of vascular complications namely retinopathy, nephropathy and cardiomyopathy) and non complicated group. Ten age and sex matched healthy children and adolescents were studied as a control group. After obtaining an informed consent all subjects enrolled in the study were subjected to: history taking, thorough clinical examination stressing on anthropometric measurements to calculate the body mass index (BMI) (data were plotted on sex and age specific charts to determine whether each subject is below or above the 85th percentile [7]), sex maturity rating to obtain the

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Tanner score [8], neurological examination, as well as fundus examination. Echocardiographic evaluation was performed using Vivid 7 Dimension, GE (Vingmed ultrasound AS N-3190 Horten, Norway), left ventricular (LV) systolic function was determined by estimation of ejection fraction (EF), LV diastolic function was determined through estimation of peak flow rate of e wave, a wave and (e/a) [9].

Laboratory investigations comprised measurement of serum creatinine, urinary microalbumin assay (immuno-turbidimetric method), glycated hemoglobin level (HbA1c) and adiponectin assay (R&D systems, Inc 614 McKisley place, N.E. Minneapolis, MN 55413, USA). This assay employs the quantitative sandwich enzyme immunoassay technique performed in microplates. Data were analyzed using SPSS.

This study was approved by the Ethical Committee of the Pediatric Department, Ain Shams University.

## RESULTS

Mean age of subjects in complicated and uncomplicated group was  $16.1 \pm 2.8$  y, and  $14.7 \pm 2.9$  y, respectively. Age of control group was  $13.1 \pm 2.9$  y. The mean duration of illness of complicated diabetics was  $10.4 \pm 2.2$  y, their glycated Hb was significantly elevated ( $10.30 \pm 1.98\%$ ). Their Tanner score ranged from 1-5 with a mean of  $3.73 \pm 1.08$ , six (40%) of them had body mass index (BMI)  $>85^{\text{th}}$  percentile.

Neuropathy occurred in 9 patients, retinopathy in 8, cardiomyopathy in one patient (ejection fraction 43%, e/a ratio 0.8), and one patient displayed only diastolic dysfunction with e/a ratio of 0.75. The mean ejection fraction in the whole group was ( $63 \pm 5.67\%$ ) and the mean e/a ratio was ( $1.6 \pm 1.37$ ). Elevated creatinine ( $4.23 \pm 2.03$ mg/dL) was found in 10 patients, all of them had albuminuria  $>30$ mg/dL and their blood pressure was controlled on ACE inhibitors. Adiponectin level was significantly elevated in complicated patients ( $10.3 \pm 5.9$  pg/mL) in comparison to the level in uncomplicated patients ( $5.04 \pm 4.3$  pg/mL) as well as the control group

( $6.5 \pm 3.7$  pg/mL) ( $P < 0.001$  and  $P > 0.1$ , respectively). Comparison between patients with and patients without complications as regards the levels of glycated Hb and adiponectin are presented in **Table I**. The single patient with established cardiomyopathy had retinopathy as well; his adiponectin was 12.5pg/dL.

Adiponectin was directly correlated with HbA<sub>1c</sub> (**Fig. 1**), and serum creatinine ( $P < 0.001$ ) and inversely correlated with the Tanner score ( $P < 0.05$ ). Within the complicated group; comparisons between those with BMI  $>$  and  $<85^{\text{th}}$  percentile, high and low Tanner score, and females and males as regard the adiponectin level are presented in **Table II**.

In the non complicated group the mean glycated Hb ( $7.80 \pm 1.73\%$ ) was significantly lower than in complicated patients ( $P < 0.05$ ). The mean duration of their illness was ( $6.5 \pm 3.5$ y). Their Tanner score ranged from 1-5 with a mean of  $3.1 \pm 1.3$ , five of them had a BMI  $>85^{\text{th}}$  percentile.

## DISCUSSION

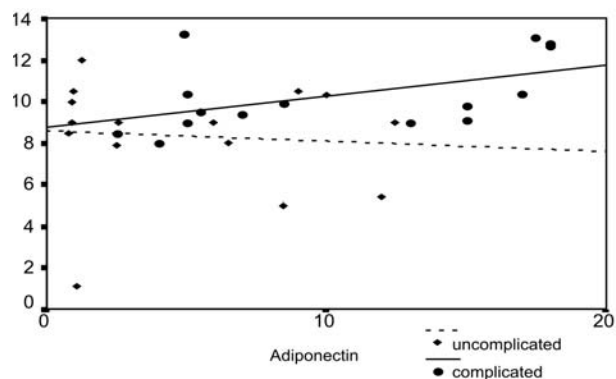
The current study showed that the adipocyte derived cytokine adiponectin was significantly high in poorly controlled diabetics with high glycated Hb. Celi, *et al.* [10] reported similar findings. The collagenous domain of the adiponectin molecule has four conserved lysines. Glycosylation of these molecules is one of the major post-translation modifications of adiponectin. In diabetic patients with constant hyperglycemia, the glycosylation process is altered, and this could lead to an altered adiponectin function. Consequently, a modified adiponectin molecule could lead to diminished negative feedback, and thus to increased adiponectin concentrations in diabetics [11].

Among the complicated group, adiponectin level was strikingly elevated in patients with nephropathy.

**TABLE I** DURATION OF DISEASE, ADIPONECTIN LEVEL AND HbA1C IN COMPLICATED AND NON-COMPLICATED DIABETICS

Variables	Absent	Present
<i>Retinopathy</i>		
Adiponectin (pg/dL)	9.7+4.6	10.9+7.1
*HbA1c %	9.2+0.6	11.3+1.9
Duration of DM (y)	11+1.7	10+2.7
<i>Neuropathy</i>		
Adiponectin (pg/dL)	11.3+6.1	9.7+6
HbA1c %	10.4+1.9	10.2+1.8
Duration of DM (y)	10+1.8	10.2+2.6
<i>Nephropathy</i>		
#Adiponectin (pg/dL)	6.8+4.2	15.7+3.7
*HbA1c %	9.6+1.5	11.3+1.7
Duration of DM (y)	10.8+1.9	10+2.9

\* $P < 0.05$ ; # $P < 0.001$ ; DM= diabetes mellitus, Y=year, Hb A1c = glycated hemoglobin.



**FIG. 1** Correlation between adiponectin and glycated hemoglobin in children with uncomplicated and complicated diabetes mellitus.

**WHAT IS ALREADY KNOWN?**

- Adiponectin levels decrease in type 2 diabetes but increases in type 1 diabetes in the presence of complications.

**WHAT THIS STUDY ADDS?**

- Levels of rise of adiponectin differs by the type of complications, and are also affected by puberty and BMI in type I diabetic children with complications.

**TABLE II** ASSOCIATION OF ADIPONECTIN LEVELS WITH BMI, SEXUAL MATURITY AND GENDER IN DIABETIC CHILDREN

Variables	Complicated group	Uncomplicated group
<i>Body Mass Index*</i>		
< 85th percentile	13.7±5.2	7±4
>85th percentile	5.4±2.1	1±0.2
<i>Tanner score<sup>#</sup></i>		
4-5	6.5±4.4	1±0.2
<4	12.9±5.4	7.7±3.6
<i>Gender</i>		
Female	5.9±4.8	12.3±5.3
Males	8.8±6.2	2.3±2.4

\* $P < 0.001$  for comparison in both complicated and uncomplicated group;  $P < 0.001$  in complicated group and  $< 0.005$  in uncomplicated group.

Saraheimo, *et al.* [12], elucidated a relationship between adiponectin and nephropathy. Renal insufficiency *per se* could stimulate adiponectin production or alternatively lead to a defect in the clearance of adiponectin. The latter suggestion is supported by the finding that successful kidney transplantation is followed by decreased adiponectin concentration [13]. Adiponectin itself may have a role in mitigating the microvascular and macrovascular burden in diabetic nephropathy. Treatment with angiotensin converting enzyme inhibitor (ACEI) was also associated with an increase in adiponectin level [14].

Adiponectin levels were also elevated in patients with retinopathy, neuropathy and in the single patient with cardiomyopathy. Hadjadj, *et al.* [15] reported that elevated adiponectin observed in subjects with microvascular and macrovascular diseases may indicated an altered regulation of this adipocytokine in patients with complications associated with type I diabetes.

Adiponectin level was normal in the studied uncomplicated diabetic patients, as also observed earlier [3,16]. Chronic exposure to insulin (as in type 2 diabetes) decreases the gene expression of adiponectin in cultured adipocytes, suggesting that absolute insulin deficiency may contribute to elevated level of serum adiponectin in type I diabetes, but appropriate regular treatment with

insulin returned these levels to normal [17].

We conclude that adiponectin levels are high in complicated type I diabetic children and adolescents especially those who developed nephropathy, and it can reflect poor glycemic control. Meanwhile, it remained normal in uncomplicated diabetics. BMI and pubertal development exert negative effect on circulating adiponectin.

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