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## **Glycemic Control Could Reverse Subclinical Atherosclerotic Changes and Normal Adiponectin Levels in Lean Type-1 Diabetic Children**

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## Glycemic Control Could Reverse Subclinical Atherosclerotic Changes and Normal Adiponectin Levels in Lean Type-1 Diabetic Children

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*Adiponectin is an anti-inflammatory, antiatherogenic, and insulin-sensitizing hormone. It inhibits neointimal media thickening and vascular smooth muscle cell proliferation. This study aimed at delineating the relation between glycemic control and adiponectin levels and its impact on carotid intima media thickness (cIMT) in lean, newly diagnosed type-1 diabetic children. 46 diabetic children were examined, their mean age was  $11.59 \pm 3.64$  years (mean duration of diabetes  $2.89 \pm 1.15$  years, mean BMI  $20.86 \pm 3.94$ , mean annual HbA<sub>1c</sub>  $7.7 \pm 1.5$ ). 46 healthy control subjects matched in age, sex, and BMI were enrolled in this cross-sectional study at the Suez Canal University Hospital pediatric outpatient clinic in Ismailia. All children had normal blood pressure for age and sex, normal lipid profile and normoalbuminuria. Adiponectin and HbA<sub>1c</sub> were measured, carotid intima media thickness was assessed. Adiponectin levels were significantly lower in children with type-1 diabetes mellitus (DM1;  $10.1 \pm 1.57$  mg) compared with controls ( $11.23 \pm 1.14$  mg;  $p = 0.02$ ). Children with DM1 had a significantly higher cIMT ( $0.55 \pm 0.06$  mm) than controls ( $0.43 \pm 0.04$  mm;  $p = 0.00$ ). Adiponectin levels correlated negatively with cIMT ( $p = 0.01$ ). Adiponectin levels showed no significant difference in children with good metabolic control (average annual HbA<sub>1c</sub>  $< 7\%$ ;  $11.51 \pm 0.45$  mg) compared to the control group ( $11.23 \pm 1.14$  mg;  $p = 0.15$ ). Adiponectin was significantly higher ( $11.51 \pm 0.45$  mg) and cIMT was significantly lower ( $0.45 \pm 0.03$  mm) in children with good metabolic control than in those with poor metabolic control ( $9.43 \pm 1.38$  mg;  $0.57 \pm 0.05$  mm). From the results it can be concluded that glycemic control may have a crucial impact on preventing atherosclerotic changes in type-1 diabetic children with a short duration of diabetes. Diabetic children with good metabolic control and a short duration of diabetes had no significant difference in adiponectin levels compared to healthy children. J Clin Basic Cardiol 2011; 14 (online): 3–6.*

**Key words:** adiponectin, type-1 diabetes, carotid intima media thickness, subclinical atherosclerosis, glycemic control

Diabetes mellitus type 1 (DM1) is a known risk factor for arterial atherosclerosis. Individuals with DM1 have a 2–4 times higher risk of developing atherosclerotic diseases [1]. The pathogenesis of this increased risk for premature heart disease in DM1 is enigmatic. Atherosclerosis is regarded as an inflammatory disease. Many studies have established adipose tissue as an endocrine organ capable of hormone and cytokine production [2]. It was discovered in 1995 [3]. A large body of evidence indicates that adiponectin has potential anti-atherogenic and anti-inflammatory properties [4, 5]. Adiponectin mimics 3 major effects of insulin: (1) it promotes increased glucose uptake and oxidation, (2) it reduces the expression of molecules involved in gluconeogenesis in the liver, and (3) it increases fatty acid oxidation in muscles through increasing molecules involved in fatty acid oxidation such as acyl coenzyme A oxidase [6]. The molecular mechanisms of vascular protective effects include inhibition of tumor necrosis factor  $\alpha$ -stimulated adhesion of monocytes to endothelial cells. Adhesion of monocytes to the vascular endothelium and the consequent transformation into foam cells may be considered fundamental for the development of vascular diseases [7]. Adiponectin inhibits the adhesion of monocytes to the endothelium and reduces the production of cytokines by macrophage phagocytosis. Adiponectin levels may be a useful marker of and a potential therapeutic target for coronary artery disease prevention [8]. This study aimed to delineate the relation between glycemic control and adiponectin levels and its impact on carotid intima media thickness (cIMT) in lean, newly diagnosed type-1 diabetic children.

### Materials and Methods

This study was a case-control study. It was performed on 46 children and adolescents with DM1 attending the Pediatric Endocrinology Clinic of the Suez Canal University, Ismailia.

The study was conducted between April 1 and November 1, 2009. 46 healthy age- and sex-matched children were included as a control group. All children were normotensive, normoalbuminuric, and had no retinopathy. Those who received regular medication that can affect carotid intima media thickness such as aspirin or cholesterol-lowering drugs were excluded. Height, weight, and Body Mass Index were measured according to the Egyptian growth curves. Pubertal maturation was assessed [9]. Good glycemic control was defined as an average annual HbA<sub>1c</sub>  $< 7\%$  and poor glycemic control as an average HbA<sub>1c</sub>  $> 9\%$ .

### Laboratory Investigation

#### Lipid Profile

Venous blood samples were taken in the morning after an overnight fast (10–12 h). Total serum cholesterol and triglyceride concentrations were measured using standard enzymatic methods [10]. Glycosylated hemoglobin (HbA<sub>1c</sub>) was determined by quantitative colorimetric determination of glycohemoglobin in whole blood [11]. Adiponectin was measured by enzyme-linked immunosorbent assay (ELISA). AviBion Human adiponectin enzyme-linked immunosorbent assay kits were used for monitoring serum adiponectin levels.

#### Carotid Artery Studies

Doppler ultrasound on carotid arteries was performed using a Philips HD11, linear array probe 12 MHz. The estimation of cIMT was done at the Radiology Department, Suez Canal University Hospital. The child was in supine position. The same experienced doctor scanned all children and used the same equipment. He was blinded to clinical and laboratory characteristics. All studies were done following a predetermined standardized scanning protocol for the right and left carotid arteries, using images of the far wall of the distal com-

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**Table 1.** Adiponectin levels and cIMT in children with DM1 and in the control group.

	Study group	Control group	p
n	46	46	–
Age (years)	13.63 ± 3.64	12.5 ± 3.02	0.14
Weight (kg)	46.65 ± 17.24	44.33 ± 11.74	0.49
Height (m)	1.47 ± 0.19	1.5 ± 0.14	0.43
BMI (kg/m <sup>2</sup> )	20.56 ± 3.54	19.32 ± 2.43	0.07
Adiponectin (mg)	10.1 ± 1.57	11.23 ± 1.14	0.03
– Prepubertal onset of DM1	10.68 ± 1.41		0.0001
– Pubertal onset of DM1	8.9 ± 0.9		
cIMT (mm)	0.56 ± 0.06	0.43 ± 0.04	0.001
– Prepubertal onset of DM1	0.53 ± 0.07		0.003
– Pubertal onset of DM1	0.59 ± 0.03		

mon carotid arteries and carotid bulbs according to the Mannheim common carotid IMT consensus [12]. Each CCA segment was measured. Four measurements of the intima media thickness were averaged to yield the mean common carotid intima media thickness for each side.

**Data Analysis**

All data were collected and statistically analyzed using SPSS 14. Numerical data were expressed as mean ± standard deviation (SD). Non-numerical data were expressed as percentage. The mean was compared using the unpaired Student’s t test. P < 0.05 was considered statistically significant. Between-group comparisons were made using ANOVA to analyze differences between cases and controls. The Pearson correlation was calculated to determine univariate relationships. Multiple regression analysis was performed to determine predictive variables for carotid IMT.

**Ethical Consideration**

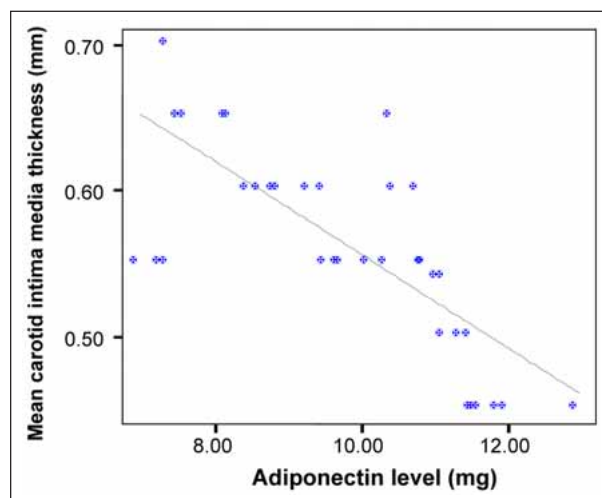
This study was performed after obtaining written parental consent.

**Results**

All subjects were matched for age, sex, and BMI, as shown in Table 1. Adiponectin levels were significantly lower in children with diabetes (10.1 ± 1.57 mg) than in the control group, their annual HbA<sub>1c</sub> was < 7 % (11.23 ± 1.14; p > 0.03). Diabetic children had a significantly higher cIMT (0.56 ± 0.06 mm) than the control group (0.43 ± 0.04; p = 0.001; Table 1).

Adiponectin levels were significantly lower (8.9 ± 0.9 mg) in children with pubertal compared with prepubertal onset of diabetes (10.68 ± 1.41 mg; p = 0.0001). Carotid intima media thickness was significantly higher (0.59 ± 0.03 mm) in children with pubertal compared with prepubertal onset of diabetes (0.53 ± 0.07 mm; p = 0.003; Table 1).

Adiponectin levels were significantly lower in diabetic children with poor metabolic control (9.43 ± 1.38 mg) than



**Figure 1.** Correlation between adiponectin and cIMT in children with DM1.

in those with good metabolic control (11.51 ± 0.45 mg; p = 0.004). Carotid intima media thickness was significantly higher in diabetic children with poor metabolic control (0.57 ± 0.05 mm) than in those with good metabolic control (0.45 ± 0.03 mm; p < 0.01). Diabetic children with good metabolic control (annual HbA<sub>1c</sub> < 7 %) had no significant difference in adiponectin levels when compared to controls (11.51 ± 0.45 mg and 11.23 ± 1.14 mg, respectively; p = 0.82; Table 2).

Carotid intima media thickness correlated negatively with adiponectin (p = 0.007; Figure 1) and positively with age (p = 0.005), age at onset of diabetes (p = 0.001), duration of diabetes (p = 0.001), and HbA<sub>1c</sub> (p = 0.002).

Multivariate regression model including cIMT as dependent variable and adiponectin, age, age at onset, duration, BMI, and HbA<sub>1c</sub> as independent variables adjusted for blood pressure, height, and total cholesterol level, the most fitting factor that can predict cIMT was adiponectin (p = 0.01), duration of DM1 (p = 0.001), and BMI (p = 0.0001). Multivariate regressions were constructed to determine factors predicting adiponectin levels as dependent variables and BMI, HbA<sub>1c</sub>, and duration of diabetes as independent variables. HbA<sub>1c</sub> represents a strong and independent determinant of adiponectin levels (p = 0.0005), followed by duration of diabetes (p = 0.01) and BMI (p = 0.03).

**Discussion**

The effect of increasing hyperglycemia on the risk of CVD mortality is more profound in type-1 than in type-2 diabetic subjects [13]. In experimental studies, adiponectin has been shown to exert anti-inflammatory, anti-atherosclerotic, and insulin-sensitizing effects, and to inhibit neointimal thicken-

**Table 2.** Adiponectin levels and cIMT in children with good and poor metabolic control, children with DM1, and in the control group.

	DM1 with poor metabolic control	DM1 with good metabolic control	Control group	p			
				Difference between groups	Poor control vs control group	Good control vs control group	Poor control vs good control
Adiponectin (mg)	9.43 ± 1.38	11.51 ± 0.45	11.23 ± 1.14	0.01	0.0001	0.15	0.004
cIMT (mm)	0.57 ± 0.05	0.45 ± 0.03	0.43 ± 0.04	0.002	0.001	0.01	0.01

ing and vascular smooth muscle cell proliferation in mechanically injured arteries [14]. The thickness of cIMT is an excellent surrogate marker of cardiovascular risk [15]. The prevalence of subclinical atherosclerosis as estimated by cIMT is significantly increased in DM1 youths relative to controls [16].

An increase of 0.2 mm of cIMT was associated with a 28-% increase in the likelihood of incident stroke. The present study showed significantly increased cIMT in diabetic children ( $0.56 \pm 0.06$  mm) compared to the control group ( $0.43 \pm 0.04$  mm;  $p < 0.001$ ). Similar results were reported by others [17–21]. These findings extend to observations of postmortem studies that have indicated a relation between early atherosclerotic vascular lesions and diabetic state [22]. The prevalence of subclinical atherosclerosis as estimated by cIMT is significantly increased in DM1 youths relative to controls [20, 23]. However, other studies were unable to demonstrate increased carotid thickening in children with a short and longer duration of diabetes [24, 25]. Differences in methodology and study population may offer an explanation for the discrepancy. Chronic states of hyperglycemia may induce atherogenesis by increasing oxidative stress leading to increased LDL oxidation [26] and decreased nitric oxide bioavailability, inducing endothelial dysfunction [27]. The present study showed a positive, statistically significant correlation between mean carotid intima media thickness and both age of diabetic subjects ( $r = 0.88$ ;  $p < 0.001$ ) and age at onset of diabetes ( $r = 0.71$ ;  $p < 0.001$ ). Carotid intima media thickness was  $0.534 \pm 0.072$  mm in prepubertal onset of diabetes versus  $0.59 \pm 0.039$  mm in pubertal onset of diabetes with a statistically significant difference ( $p < 0.001$ ). Both Atwa et al [18] and Abdelghaffar et al [19] reported a statistically significant positive correlation between mean cIMT and age of diabetic subjects. This does not suggest that early ages of onset are protective but rather that “the clock does not run as fast” for the years before pubertal onset. Donaghue et al [28] also reported that prepubertal duration of diabetes contributes less than pubertal duration to the risk of diabetic complications. The mechanism behind this effect of age at onset is not clear, but it has been speculated that puberty, characterized by both rapid growth, hormonal changes, and worsening in glycemic control, may accelerate the processes leading to chronic diabetes complications [29].

There was a statistically significant positive correlation between mean cIMT and duration of DM1 of diabetic subjects ( $r = 0.75$ ;  $p < 0.001$ ). Rodriguez et al [30], Atwa et al [18], Abdelghaffar et al [19], and Jarvisalo et al [20] also reported a positive, statistically significant correlation between mean cIMT and duration of DM1 of diabetic subjects. Prolonged exposure to hyperglycemia is recognized as the primary casual factor in the pathogenesis of diabetic complications [31, 32]. There was a statistically significant positive correlation between mean carotid intima media thickness and HbA<sub>1c</sub> of diabetic subjects ( $r = 0.81$ ;  $p = 0.001$ ). Atwa et al [18] and Abdelghaffar et al [19] also reported a statistically significant positive correlation between mean carotid intima media thickness and HbA<sub>1c</sub> of diabetic children. This explains the value of glycemic control in preventing or minimizing macrovascular complications. The study showed a significantly negative correlation between mean carotid intima media thickness and serum adiponectin levels of diabetic subjects ( $r = -0.74$ ;  $p < 0.002$ ). Adiponectin infiltrates in the subendothelial space of injured vascular walls and suppresses the expression of adhesion molecules on endothelial cells, thus inhibiting sub-inflammatory processes that occur during early phases of atherosclerosis. It also inhibits the production and action of TNF- $\alpha$  and suppresses the transformation of macrophages

into foam cells, which is the link between vascular inflammation and atherosclerosis. The cellular antiatherosclerotic effect of adiponectin is documented by its capacity to inhibit growth factors in smooth vascular musculature and reduction of macrophage migration [33]. So the ability of adiponectin to act as an anti-inflammatory and antiatherogenic factor has made this novel adipocytokine a promising therapeutic tool for the future [34]. Cardiovascular disease is the most frequent cause of death in DM1, with a 10 times, increased, CVD-related all-cause mortality compared with the general population [35, 36], despite modern advances in glycemic control and CVD risk factor modification [37, 38]. Other studies showed that adiponectin suppresses various mechanisms contributing to atherogenesis [39–42] and our results are consistent with this background. This may explain the negative correlation between mean carotid intima media thickness and serum adiponectin levels of diabetic children in our study. The study showed that the lean diabetic group had significantly lower serum adiponectin levels compared with control subjects. Adiponectin levels in the diabetic group were  $10.1 \pm 1.57$  versus  $11.23 \pm 1.14$  in the control group ( $p < 0.001$ ). Studies in DM1 children are limited and the results were controversial. Celi et al [43] found that circulating adiponectin concentrations were higher in prepubertal diabetic children compared with healthy children. Morales et al [44] found that there was no significant difference between adiponectin levels in DM1 children compared with controls. They were  $10.2 \mu\text{g/ml}$  in diabetic children versus  $10.6 \mu\text{g/ml}$  in controls. Martos-Moreno et al [45] found that, at diagnosis, adiponectin levels in prepubertal children with newly diagnosed DM1 were similar to controls; after one month, adiponectin levels increased and normalized at month 4. Abu El-Yazid et al [46] showed that serum adiponectin is lower in diabetic patients compared to control groups. This difference in adiponectin levels in children with DM1 in various studies may be due to differences in ethnic groups, methodology, population size, mean age of study population, and differences in diabetic control. The lower adiponectin levels in the present study may be explained by the fact that all children were normoalbuminuric along with ethnic variation. Adiponectin can be glycosylated and hydroxylated; consequently, modified adiponectin could lead to diminished negative feedback and thus to increased adiponectin concentrations. In the present study, there was a statistically significant negative correlation between adiponectin levels and both age of onset of diabetes ( $r = -0.78$ ;  $p < 0.0001$ ) and age of diabetic subjects ( $r = -0.89$ ;  $p < 0.002$ ). The findings of Pozza et al [47] are in agreement with our results: they found that plasma adiponectin levels (mean  $9.1 \pm 3.1 \mu\text{g/ml}$ ) were negatively correlated with the age of diabetic subjects ( $p < 0.04$ ). Our study showed a statistically significant negative correlation between adiponectin levels and duration of DM1 ( $r = -0.83$ ;  $p = 0.001$ ). Galler et al [48] found that adiponectin levels were not affected by duration of diabetes. Our study showed a significantly negative correlation between adiponectin levels and BMI of diabetic subjects ( $r = -0.72$ ;  $p < 0.004$ ). Galler et al [48] found that plasma adiponectin levels were negatively correlated with BMI. There was a statistically significant negative correlation between adiponectin levels and HbA<sub>1c</sub> of diabetic subjects ( $r = -0.89$ ;  $p < 0.001$ ). In agreement with our results, Celi et al [43] found that circulating adiponectin concentrations were higher in prepubertal diabetic children and were positively associated with HbA<sub>1c</sub>, while Galler et al [48] failed to find a significant difference of adiponectin levels regarding gender, diabetes duration, or HbA<sub>1c</sub>.



## Conclusion

Glycemic control may have crucial impact to prevent atherosclerotic changes in DM1 children with a short duration of diabetes. Diabetic children with good metabolic control and a short duration of diabetes had no significant difference in adiponectin levels when compared to healthy children.

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