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Normal Adiponectin Level and Glycemic Control could Delay Subclinical Atherosclerotic Changes 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 to delineate the relation between glycemic control and adiponectin level and its impact on carotid Intima Media Thickness (cIMT) in lean newly diagnosed type 1 diabetic children. Forty six diabetic children their mean age was (11.59±3.64 years). The mean duration of diabetes (2.89±1.15 years), the mean BMI (20.86±3.94) the mean annual HbA1c (7.7±1.5). Forty six healthy control subjects matched in age, sex and BMI are enrolled in this cross-sectional study at 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 HbA1c, were measured. Carotid intima media thickness was assessed. Adiponectin level was significantly lower in children with T1 DM (10.1±1.57 mg) than control (11.23±1.14 mg) ($p = 0.02$). Children with T1D had significantly higher cIMT (0.55±0.06 mm) than control (0.43±0.04 mm) ($p = 0.00$). Adiponectin level correlated negatively with cIMT ($p = 0.01$). Adiponectin level had no significant difference in children with good metabolic control (average annual HBA1C <7%) (11.51±0.45 mg) compared to control group (11.23±1.14 mg) ($p = 0.15$). Adiponectin was significantly higher (11.51±0.45 mg) and cIMT was significantly lower (0.45±0.03 mm) in children with good metabolic control than those with poor metabolic control (9.43±1.38 mg) (0.57±0.05 mm). From the results it can be concluded that glycemic control may have crucial impact to prevent atherosclerotic changes in type 1 diabetic children with short duration of diabetes. Diabetic children with good metabolic control and short duration of diabetes had no significant difference in adiponectin level than healthy children.

Key words: Adiponectin, type 1 diabetes, carotid intima media thickness, subclinical atherosclerosis, glycemic control

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INTRODUCTION

Type 1 diabetes is a known risk factor for arterial atherosclerosis. Individuals with type 1 diabetes have a two to four fold increase risk of developing atherosclerotic diseases (Jarvisalo *et al*., 2001). Pathogenesis of increased risk of premature heart disease in type 1 diabetes 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 (Shuldiner *et al*., 2001). Adiponectin was discovered in 1995. A large body of evidence indicates that adiponectin has potential antiatherogenic and anti-inflammatory properties (Frayn *et al*., 2003; Xu *et al*., 2003). Adiponectin mimics 3 major effects of insulin: First it promotes increased glucose uptake and oxidation, second it reduces the expression of molecules involved in gluconeogenesis in the liver and the third it increases fatty acid oxidation in muscles through increasing molecules involved in fatty acid oxidation such as acyl coenzyme A oxidase (Stern *et al*., 2007). The molecular mechanisms of vascular protective effects include inhibition of tumor necrosis factor α-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 (Luo *et al*., 2010). Adiponectin inhibits adhesion of monocytes to endothelium and reduces the production of cytokines by macrophages phagocytosis. The adiponectin level may be a useful marker of and potential therapeutic target for coronary artery disease prevention (Costacou *et al*., 2005). This study aimed to delineate the relation between glycemic control and adiponectin level and its impact on carotid Intima Media Thickness (cIMT) in lean type 1 diabetic children.

MATERIALS AND METHODS

This study was a case-control study. It was performed on 46 of children and adolescents with type 1 diabetes mellitus attending the Pediatric Endocrinology Clinic of Suez Canal University, Ismailia. The study was conducted during the period from 1/4/2009 to 1/11/2009. Forty six healthy children age and sex matched were included as control group. All children were normotensive, normoalbuminuric and had no retinopathy. Those who receive regular medications that can affect carotid intima-media thickness such as aspirin, cholesterol lowering drugs as well as children with liver and renal diseases were excluded. Height, weight and body mass index were measured according to the Egyptian growth curves. Pubertal maturation was assessed (Marshall and Tanner, 1968). Good glycemic control was defined as average annual HbA1C<7% and poor glycemic control average HbA1C>9%.

Laboratory investigation

Lipid profile: Venous blood samples were taken in the morning, after an overnight fast (10-12 h). Serum total cholesterol and triglyceride concentrations were measured using standard enzymatic methods (Kuksis and Myher, 1984). Glycosylated hemoglobin (HbA1c) was determined by quantitative colorimetric determination of glycoheamoglobin in whole blood (Gabbay *et al*., 1977). Adiponectin was measured by Enzyme Linked Immunosorbent Assay (ELISA). AviBion Human adiponectin enzyme-linked immunosorbent assay kits were used for monitoring serum adiponectin level.

Carotid artery studies: Doppler ultrasound on carotid artery using a Philips HD11, linear array probe 12 MHZ. The estimation of cIMT was done at radiology department, Suez Canal University Hospital. The child was in supine position. The same experienced doctor scanned all the children and he used the same equipment. He was blinded to study subjects concerning their 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 common carotid arteries and carotid bulbs according to the Mannheim common carotid IMT consensus (Touboul *et al*., 2007). Each CCA segment was measured. Four measurements of the intima-media thickness were averaged, in order to give the mean common carotid intima-media thickness for each side.

Ethical consideration: This study was performed with parental consent.

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

RESULTS

All subjects were matched for age, sex and BMI as shown in Table 1. Adiponectin level was significantly lower in children with diabetes (10.1±1.57 mg) than control group their annual HbA1c <7% (11.23±1.14 mg) (p>0.03). Diabetic children had significantly higher cIMT (0.56±0.06 mm) than control group (0.43±0.04 mg) (p<0.001) (Table 1).

Adiponectin level was significantly lower (8.9±0.9 mg) in children with pubertal than those 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 onset of diabetes than those with prepubertal onset of diabetes (0.53±0.07 mm) (p<0.003) (Table 1).

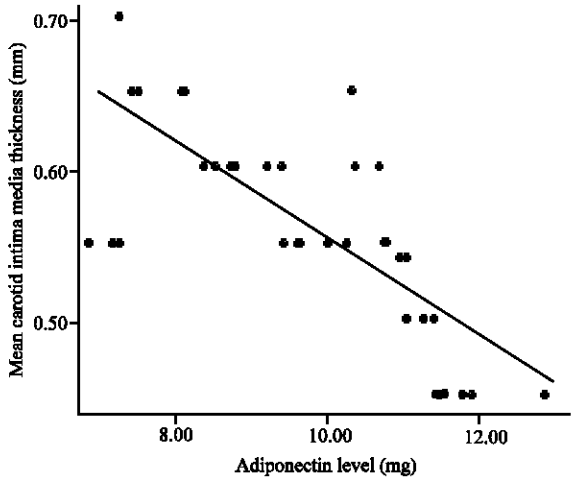

Fig. 1: Correlation between adiponectin and cIMT in children with T1D

Table 1: Adiponectin level and cIMT in children with T1D and control group

Age (year)	Study group	Control group	p-value
Weight (kg)	13.63±3.64	12.50±3.02	0.14
Height (m)	46.65±17.24	44.33±11.74	0.49
BMI (kg m^{-2})	1.47±0.19	1.50±0.14	0.43
Adiponectin (mg)	20.56±3.54	19.32±2.43	0.07
PrePubertal onset of T1D	10.10±1.57	11.23±1.14	0.03
Pubertal onset of T1D	10.68±1.41	0.43±0.04	0.0001
	8.90±0.90		
cIMT (mm)	0.56±0.06		0.001
PrePubertal onset of T1D	0.53±0.07		
Pubertal onset of T1D	0.59±0.03		0.003

Values are Mean±SD, n = 46

Adiponectin level is significantly lower in diabetic children with poor metabolic (9.43±1.38 mg) control than those with good metabolic control (11.51±0.45 mg) (p<0.004). Carotid intima media thickness is significantly higher in diabetic children with poor metabolic control (0.57±0.05 mm) than those with good metabolic control (0.45±0.03 mm) (p<0.01). Diabetic children with good metabolic control (their annual HbA1c <7%) had no significant difference in adiponectin level compared to control (11.51±0.45 mg) and (11.23±1.14 mg) (p<0.82) (Table 2).

Carotid intima media thickness correlated negatively with adiponectin (p<0.007) (Fig. 1) and age at onset of diabetes (r -0.74, p<0.001). It correlated positively with age (r 0.88, p<0.005), duration of diabetes (r 0.75, p<0.001) and HbA1c (r 0.81, p<0.002).

Multivariate regression model including cIMT as dependent variable and Adiponectin, age, age at onset, duration, BMI and HbA1c 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 T1D (<p0.001) and BMI (p<0.0001). Multivariate regression were constructed to determine factors predict adiponectin levels as dependent variable and BMI, HbA1c and duration of diabetes as independent variables. HbA1c represent a strong and independent determinant of adiponectin level (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 (Juutilainen *et al*., 2008). In experimental studies, adiponectin has been shown to exert anti-inflammatory anti-atherosclerotic and insulin sensitizing effects and to inhibit neointimal thickening and vascular smooth muscle cell proliferation in mechanically injured arteries (Goldstein and Scalia, 2004). The thickness of cIMT is an excellent surrogate marker of cardiovascular risk (Barchetta *et al*., 2009). The prevalence of subclinical atherosclerosis as estimated by cIMT is

Table 2: Adiponectin level and cIMT in children with good and poor metabolic control children with T1D and control group

				p-value			
Level	T1D with poor metabolic control	T1D with good metabolic control	Control group	Difference between group	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	0.010	0.0001	0.15	0.004
cIMT (mm)	0.57±0.05	0.45±0.03	0.43±0.04	0.002	0.0010	0.01	0.010

Values are Mean±SD

significantly increased in T1D youth relative to controls (Nadeau and Reusch, 2011).

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±0.06 mm) than the control group (0.43±0.04 mm) ($p<0.001$). Similar results were reported by others (Schwab *et al*., 2007; Atwa *et al*., 2005; Abdelghaffar *et al*., 2005; Jarvisalo *et al*., 2002; Peppa-Patrikiou *et al*., 1998). These findings extend to observations of postmortem studies that have indicated a relation between early atherosclerotic vascular lesions and diabetic state (McGill *et al*., 2000). The prevalence of subclinical atherosclerosis as estimated by cIMT is significantly increased in T1D youth relative to controls (Krantz *et al*., 2004; Jarvisalo *et al*., 2002). However, other studies were unable to demonstrate increased carotid thickening in children with a short and longer duration of diabetes (Gunczler *et al*., 2002; Parikh *et al*., 2000). Differences in methodology and study population may offer an explanation for the discrepancy. Chronic state of hyperglycemia may induce atherogenesis by increasing oxidative stress leading to increased LDL oxidation (Brownlee, 2001) and decreased nitric oxide bioavailability, inducing endothelial dysfunction (Jarvisalo *et al*., 2004). The present study showed 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±0.072 mm) in prepubertal onset of diabetes versus (0.59±0.039 mm) in pubertal onset of diabetes with statistically significant difference ($p<0.001$). Both Atwa *et al*. (2005) and Abdelghaffar *et al*. (2005) reported statistically significant positive correlation between mean cIMT and age of diabetic subjects. This suggests, not that the 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*. (2003) also reported that prepubertal duration of diabetes contributes less than the 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 (Rudberg *et al*., 1992).

There was statistically significant positive correlation between mean cIMT and duration of T1D of diabetic subjects ($r = 0.75$) ($p<0.001$). Rodriguez *et al*. (2007), Atwa *et al*. (2005), Abdelghaffar *et al*. (2005) and Jarvisalo *et al*. (2002) also reported positive statistically significant correlation between mean cIMT and duration of T1D of diabetic subjects. Prolonged exposure to hyperglycemia is recognized as the primary casual factor in the pathogenesis of diabetic complications (Laakso, 1999; The Diabetes Control and Complications Trial Research Group, 1993). There was statistically significant positive correlation between mean carotid intima media thickness and HbA1c of diabetic subjects ($r = 0.81$) ($p<0.001$). Atwa *et al*. (2005) and Abdelghaffar *et al*. (2005) also reported statistically significant positive correlation between mean carotid intima media thickness and HbA1c of diabetic children. This explains the value of glycemic control in preventing or minimizing macro-vascular complications. The study showed significant negative correlation between mean carotid intima media thickness and serum adiponectin level of diabetic subjects ($r = -0.74$) ($p<0.002$). Adiponectin infiltrates in the subendothelial space of injured vascular walls and suppress the expression of adhesion molecules on endothelial cells, thus inhibiting subinflammatory processes that occur during early phases of atherosclerosis. It also inhibits the production and action of TNF α and suppresses transformation of macrophages into foam cells that 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 (Ekmekci and Ekmekci, 2006). So, the ability of adiponectin to act as an antiinflammatory and antiatherogenic factor has made this novel adipocytokine a promising therapeutic tool for the future (Karboska *et al*., 2003). Cardiovascular disease is the most frequent cause of death in T1D, with 10-fold increased CVD-related and all-cause mortality compared with the general population (Laing *et al*., 2003; Dorman *et al*., 1984), despite modern advances in glycemic control and CVD risk factor modification (Rewers, 2008; Soedamah-Muthu *et al*., 2006). Other studies showed that adiponectin suppresses various mechanisms contributing to atherogenesis (Ouchi *et al*., 2001, 2003, 2004; Arita *et al*., 2002) and present results are consistent with this background. This may explain the negative correlation between mean carotid intima media thickness and serum adiponectin level of diabetic children in our study. The study showed that lean diabetic group had significantly lower serum adiponectin level compared with control subjects. Adiponectin level in diabetic group was (10.1±1.57) versus (11.23±1.14) in control group ($p<0.001$). Studies in T1D in children are limited and the results were controversial. Celi *et al*. (2006) found that circulating adiponectin concentrations were higher in the prepubertal diabetic children compared with healthy children.

Morales *et al.* (2004) found that there was no significant difference between adiponectin levels in T1D children compared with control. It was (10.2 μg mL^{-1}) in diabetic children versus (10.6 μg mL^{-1}) in control. Martos-Moreno *et al.* (2006) found that adiponectin levels in prepubertal children with newly diagnosed T1D were similar at diagnosis to controls, after one month adiponectin level increased and normalizing at the fourth month. Abu El-Yazid *et al.* (2008) showed that serum adiponectin are lower in diabetic patient compared to control group. This difference in adiponectin levels in children with type 1 diabetes in various studies may be due to differences in ethnic groups, methodology, population size, mean age of study population and difference in diabetic control. The lower adiponectin level in the present study may be explained by that all children were normoalbuminuric along with ethnic variation. Adiponectin can be glycosylated and hydroxylated, consequently, a modified adiponectin could lead to diminished negative feedback and thus to increased adiponectin concentrations. In the present study there was statistically significant negative correlation between adiponectin level and both age of onset of diabetes of diabetic subjects ($r = -0.78$) ($p<0.0001$) and age of diabetic subjects ($r = -0.89$) ($p<0.002$). Pozza *et al.* (2007) findings is in agreement with our results, found that plasma adiponectin level (mean 9.1±3.1 μg mL^{-1}) was negatively correlated with age of diabetic subjects ($p<0.04$). Present study showed statistically significant negative correlation between adiponectin level and duration of T1D ($r = -0.83$) ($p<0.001$). While Galler *et al.* (2007) found that adiponectin level was not affected by duration of diabetes. Present study showed significant negative correlation between adiponectin level and BMI of diabetic subjects ($r = -0.72$) ($p<0.004$). Galler *et al.* (2007) found that plasma adiponectin level was negatively correlated with BMI. There was statistically significant negative correlation between adiponectin level and HbA1c of diabetic subjects ($r = -0.89$) ($p<0.001$). In agreement with our results, Celi *et al.* (2006) found that circulating adiponectin concentrations were higher in the prepubertal diabetic children and were positively associated with HbA1c. While, Galler *et al.* (2007) failed to find significant difference of adiponectin levels regarding gender, diabetes duration or HbA1c.

CONCLUSION

Glycemic control may have crucial impact to prevent atherosclerotic changes in type 1 diabetic children with short duration of diabetes. Diabetic children with good metabolic control and short duration of diabetes had no significant difference in adiponectin level than healthy children.

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