The Egyptian Journal of Hospital Medicine (January 2014) Vol. 54, Page 88–93

Adipokines in Type 1 Diabetes Mellitus

Mohamed Al Saeed*, Nihad Al Nashar,Sahar M Al Nefaie***
Hala A Mohamed, Mohamed Ahmed***, Nesreen Al Margushi******
Department of Surgery, Taif University*, Department of Pathology, Taif University**,
Department of Radiology, Jazan University ***, Department of Medicine, Taif University******

Abstract

Background and aim of the study: Leptin, resistin and adiponectin are the most important adipokines which are influenced by body fat status, and their levels are closely related to vascular dysfunction. This study aimed to estimate the concentration of serum adiponectin and leptin in type 1 diabetic children and to find their relationship to body mass index (BMI) and microvascular complications.

Material and method: Weight (kg), height (m), BMI (kg/ m^2) , random blood sugar, mean HbA1c, urinary microalbuminurea, serum adiponectin and leptin concentration were assessed in 60 children (34 males, 26 females) with type 1 diabetes and 60 healthy control children. Medical history, clinical examination, anthropometric and pubertal assessment were done for the patients and controls. The diabetic patients were classified depending on the pubertal stage into pre-pubertal group and pubertal group, and according to gender into male group and female group.

Results: The results obtained showed significantly elevated of random blood glucose, HbA1c ($p<0.001$), total cholesterol & low density lipoprotein (LD-L) ($p<0.05$), BUN ($p<0.001$), creatinine ($p<0.05$), urinary microalbuminurea ($p<0.001$), serum adiponectin and leptin values ($p<0.001$) in type 1 diabetes children than control. In patients suffering from microvascular diabetic complications as nephropathy and neuropathy, serum adiponectin and leptin levels showed highly significant increase. The level of both adipokines was significantly increased with the increase in body mass index (BMI).

Conclusion: Serum adiponectin and leptin concentrations increase significantly in diabetic children especially in those with increase in body mass index (BMI), than healthy control and in females than males; puberty has no significant effect on their levels. Increase serum adiponectin and leptin concentrations were associated with impairment of renal functions and neuropathy and they can be used as marker for these complications.

Key words: Adipokines, Type 1 Diabetes Mellitus.

Introduction

Type 1 diabetes (T1D) accounts for about 5-10% of all cases of diabetes and its incidence is increasing worldwide [1, 2].Adipose tissue is an endocrine organ secreting several hundreds of adipokines, and altered secretion of these adipokines is a marker of adipose tissue dysfunction with expected increased risks of insulin resistance, Type 2 diabetes, fatty liver disease, hypertension, dyslipidemia, endothelial dysfunction, and atherosclerosis [3, 4]. Microvascular complications as neuropathy and nephropathy are major complications of diabetes and it was suggested that vascular risk profile such as anthropometric parameters; lipid profile and adipose tissue derived hormones (specifically, leptin and adiponectin) all impact the development of these complications[4]. Adiponectin shares in the regulation of lipid and glucose metabolism and it is suggested to play a role in prevention of atherosclerosis [5, 6]. Diagnostic usage of adiponectin was a subject of increasing interest in recent years [7]. Many authors reported that that in these conditions an elevated adiponectin level may be beneficial in reducing the risk of microvascular complications among type 2 diabetes patients. [8]. Leptin is a polypeptide hormone synthesized predominantly by the adipocyte and is thought to act as an afferent satiety signal regulating weight through suppressing appetite and stimulating energy expenditures [9]. Leptin was found to increase the peripheral insulin sensitivity and increase the vasomotor sympathetic activity through the activation of leptin receptors (OB-R) in the ventromedial and dorsomedial hypothalamic regions and exerts a direct vasodilatation through different mechanisms, which include the release of endothelial nitric oxide (NO), as well as the inhibition of the Ang II-induced calcium increase and vasoconstriction in the vascular smooth muscle layer [10].In children with type 1 diabetes, the relationship between adiponectin, leptin, and the presence of microvascular complications is not clearly

DOI: 10.12816/0002434

known [3, 4]. This study aimed to estimate the concentration of serum adiponectin and leptin in type 1 diabetic children and to find their relationship to body mass index (BMI) and microvascular complications.

Material and Methods

This study included 60 children previously diagnosed as type 1 diabetic subjects .They were enrolled from the outpatient clinics of Pediatric Hospital, Ain Shams University, Cairo, Egypt and King Abdul Aziz Specialist Hospital, Taif, Saudi Arabia; from July 2011 to July 2013. The study was approved by the ethics committees of both hospitals. Their ages ranged between 5.8-17.7 years. Another 60 healthy children who were age and sex matched served as control group. Their ages ranged between 6.7-17.9 years. All type 1 diabetic patients met the criteria of American Diabetes Association (ADA) [11], for type 1 diabetes (polyurea, polyphagia, polydepsia, loss of weight and easily fatigue). None of type 1 diabetic patients were receiving any medications, other than insulin. Informed consents were obtained from parents of all children participating in this study before enrollment in the study. All subjects in this study were divided into two groups. Group I; included diabetic children and adolescents, they were 60 patients (26 females and 34 males). Group II: included the 60 healthy children and adolescents, age and sex matched with the patient's group, without any clinical conditions involving the endocrine metabolic system (30 females and 30 males). Group I was further subdivided according pubertal stage (depending on Tanner score): into pre-pubertal group they are 20 children with mean age 9.20±1.9 years (they are Tanner I and II) and pubertal group they are 40 children with mean age 13.40±2.67,years they are Tanner (IV, V.) and sex: into male groups (n=34) and female group (n=26). All patients and control were subjected to the following; Careful history including; diabetic duration, treatment, history of hypoglycemic or hyperglycemic attack and files were revised for the number of hospital admission during the last 2 years prior to the study. History suggestive of chronic diabetic complications as: peripheral neuropathy manifestations: tingling, numbness and paraesthesia. Examination; thorough clinical examination was done with emphasis on; age, gender, body weight in kg, height in meters, and BMI (kg/ m^{2}). Neurological examination included sensory and motor nerves for diagnosis of diabetic neuropathy. Pubertal stages and sexual maturation were assessed according to Tanner classification [12, 13]. Testicular volume was evaluated by the Prader's orchidometer. Blood pressure was measured after 10 minute of rest.

Laboratory investigations: included random blood glucose,measurement of mean HbA1C% during the period of study using quantitative calorimetric determination of glycohemoglobin in whole blood, measuring blood urea nitrogen and serum creatinine, quantitative determination of urinary microalbumin for diabetic nephropathy, lipid profile including: serum total cholesterol, High density lipoprotein (HDL – Cholesterol) andlow density lipoprotein (LDL – Cholesterol) were measured, measurement of serum adiponectin, and serum leptin was determined.

Statistical analysis: Statistical tests were done using SPSS version 15. All data were expressed as mean ±standard deviation in the different groups. The results were considered significant whenever p values <0.05 and highly significant when p values <0.001. Z –score was used to assess weight-for-age, height-for-age, and weight-for-height for each participant. Means of anthropometric data as well as biochemical and hormonal concentrations were compared by Student`s "t" test. Relationships between different quantitative parameters were assessed by simple linear regression analysis ,and Pearson (r) correlation coefficients were presented.

Results

Table (1) shows that no significant difference between patients and control as regard weight, height and BMI. On the other hand, random blood glucose level, HBA1c percentage, lipid profiles serum adiponectin and urinary microalbumin displayed highly significant increase ($p<0.001$) while, serum leptin was significantly increased ($p<0.05$) in diabetic children than controls.

Table (2) there is no significant variation between patients in Tanner stages (I, II) and stages (IV, V) as regard serum adiponectin level. However, in girls, serum leptin concentrations increased accordingly during pubertal development. In boys, leptin levels increased only until Tanner stage 2 and

decreased until the end of puberty (Tanner IV, V).

Table (3) shows comparison between diabetic children with or without complication according to their mean level of adiponectin and leptin.

In table (4), the level of both adipokines was significantly increased with the increase in body mass index (BMI), the table shows also significant positive correlation between serum levels of adiponectin and leptin with HbA1c%, fasting blood glucose, and microalbuminurea in diabetic children.

Discussion

Adiponectin and leptin mediate insulin action improving peripheral insulin sensitivity with inverse relation to insulin-resistance and show lower levels in obesity and type 2 diabetes[4]. The current study proved that serum leptin and adiponectin are significantly elevated in T1D children versus healthy controls; this may be due to the increased amount of body fat in those patients. Another explanation suggested that long-term administration of insulin increases leptin through its direct effect on adipocytes [8, 9]. Serum adiponectin and leptin concentrations are regulated by adipose tissue distribution, exercise, fat mass, gender and insulin [3-5, 9]. However, Lo et al. [14], did not find that insulin had an effect on serum leptin concentration in children with diabetes. Conflicting results in this area might be due to the differences in the doses and duration of insulin treatment, caloric intake and metabolic control in the group of children. Previous study demonstrated that total serum adiponectin concentrations were higher in type 1 diabetic children than healthy control [3, 14].

No significant difference in mean serum adiponectin levels in different Tanner stages in type 1 diabetic male and female patients in the current study. This is because mean serum levels of adiponectin in males with type 1 diabetes decrease during puberty and were significantly lower at the end of puberty compared with the pre-pupertal stages in females with type one diabetes, where mean serum levels of adiponectin showed no significant change during puberty so no significant difference between adiponectin concentrations in males and females with type 1 diabetes was seen at different tanner stages [15-17].

In the present study, boys with T1D displayed higher adiponectin concentration at Tanner stage I and II and were lower in Tanner stage IV and V. On the contrary, in females adiponectin concentration showed no significant changes during puberty, this is because adiponectin levels were inversely correlated with androgen concentrations (particularly testosterone in boys) [16].

The results of this study demonstrated that diabetic children had significant increase in the weight evidenced by higher weight-for-age ($p<0.001$) and weight-for-height ($p<0.05$) indices versus the control group. Meanwhile, the height-for-age did not show any differences between the two studied groups. These results agreed with the results obtained by Lo et al. [14], who added that, insulin is a well- known anabolic hormone with lipogenic action. It causes a significant increase in body weight and body mass index and this may be the cause of theincrease of the BMI with age in their studied diabetic children. A significant positive correlation was observed in the present study between leptin and weight- for- height. Leptin level in T1D shows a dependency on adipose tissue and age, thus, it is hypothesized that the elevated BMI- adjusted leptin level in children with T1D could indicate either that these patients may be over substituted by the intensified insulin therapy that they are receiving or that their body composition and body fat content differ from that of healthy children in the sense that they have a relative increase fat mass [4, 14].

This study also revealed a significantly greater serum leptin concentration in both healthy and diabetic females than in males. The same result was obtained by other studies [4, 18-20].

Adipose tissue is a source of several adipocytokines that may contribute to vascular complications. The pathogenesis of vascular complications in T1D is poorly understood but may involve chronic-low grade inflammation [3, 14]. In the current study we found significant increase in serum adiponectin and leptin in T1D with nephropathy and neuropathy than without. Previous studies showed that adiponectin and leptin total levels were higher in type 1 diabetic patients with than without microvascular complications [3, 4, 10, 14].

Fujita et al.,[21] found that high serum adiponectin concentration was associated with the occurrence of microalbuminurea in patients

with type 1 diabetes and normoalbuminurea at the base line. This observation suggests that adiponectin may in fact promote development and progression of diabetic nephropathy. Other studies demonstrated that high serum adiponectin levels decreased after renal transplantation, suggesting that renal insufficiency may either had an effect on the clearance of adiponectin and or had stimulatory effect on adiponectin production [(22)].

The diabetic patients in the present study had hyperglycemia and increase glycylatedhaemoglobin (HbA1c percentage) which lead to increase in the production of biologically highly active molecular weight adiponectin which can be associated with the progression of diabetic nephropathy, also, HbA1c percentage may alter the action of insulin on adiponectin this may lead to an increase in adiponectin as blood glucose rises [(23)].

The present study showed that total serum cholesterol, high density lipoprotein (HD-L) and low density lipoprotein (LD-L) were significantly increased in diabetic patients than control and in female patients than male patients. This could be due to increased fatty acid oxidation by adiponectin [(24)].

Conclusion: Serum adiponectin and leptin concentrations increase significantly in diabetic children especially in those with increase in body mass index (BMI), than healthy control and in females than males; puberty has no significant effect on their levels. Increase serum adiponectin and leptin concentrations were associated with impairment of renal functions and neuropathy and they can be used as marker for these complications.

References

1. **Alqurashi KA, Aljabri KS, Bokhari SA (2011).** Prevalence of diabetes mellitus in a Saudi community. Ann Saudi Med.,31(1): 19–23.
2. **Van Belle TL, Coppieters KT, von Herrath MG (2011).** Type 1 diabetes: etiology, immunology, and therapeutic strategies. Physiol Rev., 91:79–118.
3. **Al Saeed M (2013).** The utility of adiponectin and nitric oxide metabolites as biomarkers for prediction and follow-up of vascular complications in children with type 1 diabetes mellitus. Saudi J Health Sci.,2:156-60.
4. **Blüher M (2013).** Importance of adipokines in glucose homeostasis. Diabetes Management,3: 389-400.
5. **Zhang P, Wang Y, Fan Y, Tang Z, Wang N (2009).** Overexpression of adiponectin receptors potentiates the antiinflammatory action of sub effective dose of globular adiponectin in vascular endothelial cells. ArteriosclerThrombVasc Biol., 29: 67-74.
6. **Li F, Zhao T, Wen X (20011).** Changes in serum adiponectin concentrations and endothelial function after intensive insulin treatment in people with newly diagnosed type 2 diabetes: A pilot study. Diabetes Res ClinPract., 94:186-92.
7. **Habeeb NM, Youssef OI, Saab AA, El Hadidi ES (2012).** Adiponectin as a marker of complications in type I diabetes. Indian Pediatr., 49:277-80.
8. **Kotani K, Tsuzaki K, Taniguchi N, Sakane N(2013).** Correlation between reactive oxygen metabolites and atherosclerotic risk factors in patients with type 2 diabetes mellitus. Indian J Med Res., 137:742-8.
9. **Kiess W, Anil M, Blum WF, Englaro P, Juul A, Attanasio A, Dötsch J &Rascher W (1998).** Serum leptin levels in children and adolescents with insulin-dependent diabetes mellitus in relation to metabolic control and body mass index. Eur J Endocrinol., 138: 501-9.
10. **Sowers JR (2003).** Obesity as a cardiovascular risk factor. Am J Med; 8: 115: 37-41.
11. **American Diabetes Association (2013).** Diagnosis and classification of diabetes mellitus. Diabetes Care, 36: 67-74.
12. **Marshall WA, Tanner JM (1969).**"Variations in pattern of pubertal changes in girls". Arch. Dis. Child., 44: 291–303.
13. **Marshall WA, Tanner JM (1970).** "Variations in the pattern of pubertal changes in boys". Arch. Dis. Child., 45: 13–23.
14. **Lo HC, Lin SC, Wang YM(2004).**The relationship among serum cytokines, chemokine, nitric oxide, and leptin in children with type 1 diabetes mellitus.Clin Biochem.,37: 666-72.
15. **Böttner A, Kratzsch J, Müller G, Kapellen TM, Blüher S, Keller E, et al. (2004).**Gender differences of adiponectin levels develop during the progression of puberty and are related to serum androgen levels. J ClinEndocrinol Metab.,89:4053-61.
16. **Galler A, Gellbrich G, Kratzsch J, NoackN, Kapellen T, Kiess W (2007).** Elevated serum levels of adiponectin in children, adolescents and young adults with type 1 diabetes and the impact of age, gender, body mass index and metabolic control: A longitudinal study. Eur J Endocrinol., 157:481-9.
17. **Jeffery AN, Murphy MJ, Mectalf BS, Hosking J, Voss LD, English P, et al (2008).** Adiponectin in childhood. Int J Pediatr Obes.,3:130-40.
18. **Flück CE, Kuhlmann BV, Mullis PE (1999).** Insulin increases serum leptin concentrations in children and adolescents with newly diagnosed type

I diabetes mellitus with and without ketoacidosis. Diabetologia, 42: 1067-70.

19. **Ahmed ML, Ong KK, Watts AP, Morrell DJ, Preece MA, Dunger DB (2001).** Elevated leptin levels are associated with excess gains in fat mass in girls, but not boys, with type 1 diabetes: longitudinal study during adolescence. J ClinEndocrinolMetab., 86: 1188-93.
20. **Blum WF, Englaro P, Hanitsch S, Juul A, et al. (1997).** Plasma leptin levels in healthy children and adolescents: dependence on body mass index, body fat mass, gender, pubertal stage, and testosterone. J ClinEndocrinolMetab., 82: 2904-10.
21. **Fujita H, Morii T, Koshimura J, Ishikawa M, Kato M, Miura T, et al (2005).** Possible relationship between adiponectin and renal tubular injury in diabetic nephropathy. EndocrJ.,53: 745-52.
22. **Chudek J, Adamczak M, Karkoszka H, Budzin ` ski G, Ignacy W, Funahashi T, et al (2003).** Plasma adiponectin concentration before and after successful kidney transplantation. Transplant Proc., 35: 2186-9.
23. **Shalitin S, Phillip M, (2012).**Which factors predict glycemic control in children diagnosed with type 1 diabetes before 6.5 years of age?.ActaDiabetol; 49:355-62.
24. **Giacco F, Brownlee M (2010).** Oxidative stress and diabetic complications. Circ Res., 29: 1058-70.

TABLES

Table (1): Demographic data and laboratory biomarkers (mean ± SD) of type I diabetic children and controls

	Controls (n= 60)	Diabetic children (n= 60)
Age (years) p-value	11.15 ± 3.19	12.47±3.03 >0.05
Sex M F	10 10	12 13
Weight (kg) p-value	47.45 ± 9.90	45.62 ± 6.94 >0.05
Height (Meter) p-value	1.59 ± 13.71	1.47 ± 9.45 >0.05
BMI (Kg/m^2) p-value	22.37 ± 1.78	20.35 ± 1.67 >0.05
Random glucose (mg/dl) p-value	81.50 ± 7.41	223.14 ± 67.59 <0. 001
Hb1Ic % p-value	5.09 ± 0.93	11.32 ± 4.10 <0.001
Cholesterol (mg/dl) p-value	110.25 ± 11.35	209.44 ± 29.70 <0.05
LDL (mg/dl) p-value	88.30 ± 9.44	101.55 ± 63.22 <0.05
HDL (mg/dl) p-value	38.48 ± 7.01	29.05 ± 17.55 >0.05
BUN (mg/dl) p-value	13.83 ± 2.20	18.50 ± 9.42 <0.001
Creatinine (mg/dl) p-value	0.7 ± 0.21	1.1 ± 0.34 <0.05
Microalbuminurea (µg/ml)	6.66 ±3.02	89.55 ± 30.44 <0.001
Serum adiponectin (µg /ml) p-value	10.88 ± 1.33	17.60 ± 3.00 <0.001
Leptin (ng/ml) p-value	5.69±1.67	7.48 ±1.86 <0.05

p>0.05: is considered non significant P<0.05: is considered significant

Table (2): Mean serum adiponectin levels in different Tanner stages in type 1 diabetic male and female patients

Serum adiponectin	Tanner stage				F-value	p-value
	T1	T2	T4	T5		
Diabetic male	12.30	12.80	11.80	10.45	0.95	>0.05
Diabetic female	13.20	16.25	15.74	14.93	1.45	>0.05
Serum leptin						
Diabetic male	5.99	7.19	5.76	4.05	2.11	<0.05
Diabetic female	6.11	8.56	9.12	10.28	4.34	<0.001

Table (3): Comparison between diabetic children with or without complication according to their mean level of adiponectin and leptin

Diabetic complication	Serum adiponectin (µg /ml)	Serum leptin (ng/ml)
Without microalbuminurea (n=15)	11.06 ± 3.20	10.32 ±1.09
With microalbuminurea (n=10)	17.00 ± 4.05 <0.05	14.24 ± 2.88 <0.05
Without neuropathy (n=16)	12.16 ± 4.10	10.56 ± 1.90
With neuropathy (n=9)	16.55 ± 3.60 <0.05	16.24 ±2.98 <0.001

Table (4): Correlations between serum adiponectin with demographic data in patients with T1DM

	Age	BMI	F. bl. glucose (mg/dl)	HbAc1 %	Microalbuminurea
Serum adiponectin r= p<	- 0.0263 >0.05	- 0.4987 <0.05	0.1009 >0.05	0.7500 <0.001	0.6179 <0.001
Serum Leptin r= p<	0.580 8 <0.05	0.673 8 <0.05	0.6441 <0.05	0.6966 <0.05	0.4512 <0.05