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Study of Visfatin Level in Type 1 Diabetic Children and Adolescents

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Keywords: Type 1 diabetes; Visfatin; complications; microalbuminuria.

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Abstract

BACKGROUND: Visfatin is an intracellular enzyme, known as nicotinamide phosphoribosyltransferase (Nampt) and pre-B-cell colony-enhancing factor (PBEF-1). It has insulin-mimetic effects and lowers plasma glucose levels.

AIM: The aim of the work was to assess serum concentration of Visfatin in type 1 diabetic children and adolescents and study its relationships with duration of diabetes, body mass index (BMI), glycemic control, insulin dosage, lipid profile and microvascular complications.

MATERIAL AND METHODS: Fifty children and adolescents with type 1 diabetes mellitus were recruited with 30 ages and gender-matched healthy subjects. They were subjected to history taking; anthropometric measurements and chronic diabetic complications were recorded if present. Laboratory analysis included urinary microalbumin, serum triglycerides, HDL, LDL, cholesterol, fasting blood glucose, glycosylated Hb (HbA1c) and serum visfatin which was measured with enzyme-linked immunosorbent assay.

RESULTS: Diabetic patients showed highly significant decrease in the level of visfatin compared to the control group (P = 0.0001).There was significant further decrease in visfatin level in diabetics with microalbuminuria (n = 13) compared to normoalbuminuric patients (n = 37) (P = 0.015). There was highly significant inverse correlation between visfatin level with age (r = -0.379, p = 0.007), BMI (r = -0.418, p = 0.003), waist circumference (r = -0.430, p = 0.002), hip circumference (r = -0.389, p = 0.005) and microalbuminuria (r = -0.323, p = 0.022).

CONCLUSIONS: Type 1 diabetic children and adolescents had a significantly lower visfatin level compared to controls. A marked decrease in the level of visfatin was shown in patients with microalbuminuria with an inverse correlation with BMI suggesting an important role of visfatin in the pathogenesis of type 1 diabetics and type 1 diabetic nephropathy.

Introduction

Children with prolonged hyperglycemia in Type 1 diabetes are exposed to long-term dysfunction, and failure of various organs especially the eyes, kidneys, and blood vessels [1]. Visfatin is a ubiquitous intracellular enzyme, known as nicotinamide phosphoribosyl transferase (NAMPT) and pre-B-cell colony-enhancing factor (PBEF-1). It is also identified as a novel adipocytokine [2]. It is preferentially produced in visceral adipose tissue and expressed in the isolated subcutaneous adipose cells as well. Both tissue expression and plasma levels of visfatin increase in parallel with obesity. Visfatin has insulin-mimetic effects and lowers plasma glucose levels [3, 4]. Also, high glucose levels markedly increased visfatin synthesis in cultured adipocytes [5]. Moreover, circulating visfatin concentrations were shown to increase in parallel with hyperglycemia [6]. It was first reported that patients with uncomplicated type 2 diabetes mellitus had elevated plasma visfatin levels [7]. Conversely, plasma visfatin levels were reported to be decreased in women with gestational diabetes mellitus (DM) [6]. Visfatin expression and plasma levels of visfatin were associated with obesity, insulin resistance and the level of albuminuria in type 2 diabetic patients [8]. Previous work is studying visfatin levels in populations with abnormal glucose metabolism which was not primarily associated with insulin resistance, like type 1 DM, are very limited [4, 6, 9]. The aim of this work was to assess plasma concentration of visfatin in type 1 diabetic children and adolescents in comparison with healthy controls. Further, the possible relationships between visfatin and duration of diabetes, body mass index (BMI), glycemic control, insulin dosage, lipid profile and microvascular complications were investigated.

Materials and Methods

Fifty children and adolescents previously diagnosed with type 1 diabetes mellitus were recruited from the Pediatric Diabetic Clinic, Children's Hospital, Ain Shams University together with 30 age and sex-matched healthy children and adolescents served as the control group. The age range for screened subjects was between 6 and 16 years old. They had disease duration of 5.63 ± 3.79 years with range (1-15 years). Exclusion criteria: chronic renal disease, chronic liver disease, heart failure, acute or chronic infections, malignancy. The study's protocol was approved by the ethical and research committee of the Council of Faculty of Medicine, Ain Shams University as well as by the ethical committee of the National Research Centre. Consents were taken after an explanation of the study and before the initiation of the research study.

Methods

Children were subjected to history taking to fulfill needed data: Insulin therapy, regarding dose in units/kg and type, history suggestive of acute metabolic complications, as hypoglycemic attacks (sweating, headache, blurring of vision, tremors, convulsions, and coma), diabetic ketoacidosis (DKA), history suggestive of chronic diabetic complications as ocular manifestations (persistent blurring of vision flashes of light), Peripheral neuropathy manifestations (tingling, numbness and paresthesia), clinical examination with special emphasis on anthropometric measures as wt, ht, and Standard deviation score (SDS) of height for age and weight for height [10].

Body Mass Index (BMI) was calculated by applying the formula: BMI = weight in kg/ (height in m²). Once BMI is calculated for a child or adolescent, it is plotted by age on the Egyptian sex-specific growth chart. According to the Center for Disease Control and Prevention [11]: Severe obesity: BMI ≥97th percentile for their age; Obese: BMI is ≥95th percentile for their age; Overweight: BMI ≥85th percentile and below the 95th percentile; Normal weight: BMI ≥5th percentile and below the 85th percentile.

Laboratory investigations

Evaluation of Urinary microalbumin was done by using the SERA-PAK immune-microalbumin kit (Bayer Corporation Benedict Ave, Tarry Town, NY, USA). Persistent microalbumin excretion rate of 30-300 mcg/mg creatinine by an immune turbid metric method in 3 repeated samples. It is used to assess the presence of nephropathy [12].

Serum Sample Collection

About 5 cc venous blood were withdrawn from each child after overnight fasting (about 8-12 hrs.). After separation of serum, the following laboratory tests were done: Determination of complete lipid profile (serum triglycerides, HDL, LDL cholesterol).

Fasting blood glucose was assessed using the enzymatic method on Hitachi instrument [13]. Glycosylated Hb (HbA1c) was measured using HPLC (high purified liquid chromatography) [14]. Then serum was divided into aliquots and kept at -20°C till used for the determination of serum visfatin. Serum visfatin was assessed by Enzyme Linked Immunosorbent Assay (ELISA). This kit was supplied by Glory Science.

Statistical Analysis

The standard computer program Statistical Package for Social Science (IBM SPSS) version 21 was used for data entry and analysis. The comparison between groups with qualitative data was done by using Chi-square test and Fisher exact test instead of Chi-square only when the expected count in any cell found less than 5%. The comparison between two independent groups with quantitative data and parametric distribution were done by using an independent t-test, while the comparison between more than two groups was done by using One-Way Analysis of Variance (ANOVA). Spearman correlation coefficients were used to assess the relation between two quantitative parameters in the same group and also partial correlation was used to assess the relation between two parameters in the same group after adjusting the effect of other parameters. The p-value was considered significant if $P < 0.05$.

Results

As regard visfatin, there was a highly significant decrease in the level of serum visfatin in the diabetic patients' group than the control group. The mean serum level of visfatin in control is (28.71 ± 8.27), calculating the lower cut point = Mean - 2 S.D = 12, so our cases were considered to have a physiologically low visfatin level if < 12 (ng/ml).

The study showed that 24 patients (48%) had visfatin level <12 (ng/ml), while 26 patients (52%) had visfatin level ≥ 12 (ng/ml). It also showed that the median of visfatin level in type 1 diabetic patients was 12.05 (Table 1).

The distribution of microalbuminuria in 13 patients (26%), neuropathy in 8 patients (16%) and retinopathy in 3 patients (6%) among the type 1 diabetic patients group is shown in Table 2. There

was a significant increase in age, DM duration, insulin dose, BMI, waist/ht, Ht SD, cholesterol level, HDL, LDL microalbuminuria and a decrease in visfatin level in diabetic patients with complications (Table 2).

Table 1: Comparison between type 1 diabetic patients versus healthy subjects regarding growth and laboratory results

	Patients group N=50		Healthy subjects group N=30		Independent t-test	
	Mean	SD	Mean	SD	t	P- value
Ht. sds	-0.31	1.06	0.09	1.26	1.510	0.135
Wt. sds	1.10	1.64	1.45	1.62	0.909	0.366
Triglyceride (mg/dL)	77.76	24.79	62.63	22.97	-2.714	0.008
Cholesterol(mg/dL)	175.40	30.85	150.73	20.46	-3.891	0.0001
HDL (mg/dL)	51.40	14.56	47.33	16.84	-1.140	0.258
LDL (mg/dL)	109.72	31.43	95.00	14.53	-2.411	0.018
HbA1c (gm%)	8.82	1.38	4.59	0.23	-16.564	0.0001
Visfatin (ng/ml)	Patients group N=50		Healthy subjects group N=30		Independent t-test	
	Mean ± SD	Range	Mean ± SD	Range	t	P-value
	11.26 ±5.84	0.1 –25.10	28.71±8.27	15 – 47.6	11.040	0.0001

Ht = height, Wt = weight, HDL = high density lipoproteins, LDL = low density lipoproteins, HbA1c = glycated haemoglobin.

There was significant increase regarding age, duration, insulin dosage, height SDS, BMI, waist, hip and waist to hip in microalbuminuric patients than that in normoalbuminuric (Table 3).

Table 2: Effect of presence of complications of Type I DM on different studied parameters

	1=No Complications 2= With Complications	No	Mean	Std. Deviation	Sig. (2-tailed)
Age	1	36	11.00	3.16	0.000
	2	14	15.14	2.18	
T1DM Duration Years	1	36	4.10	2.85	0.000
	2	14	9.57	3.03	
Insulin dose	1	36	0.94	0.23	0.020
	2	14	1.12	0.24	
BMI	1	36	19.12	3.53	0.001
	2	14	22.82	3.22	
Waist/Hip	1	36	0.83	0.05	0.394
	2	14	0.82	0.05	
Waist /HT	1	36	0.45	0.03	0.003
	2	14	0.48	0.05	
Ht SD	1	36	-0.10	1.05	0.021
	2	14	-0.86	0.93	
Wt SD	1	36	1.10	1.78	0.983
	2	14	1.11	1.26	
Triglycerides (mg/dL)	1	36	75.22	18.65	0.250
	2	14	84.29	36.29	
Cholestero l(mg/dL)	1	36	169.72	25.41	0.035
	2	14	190.00	39.11	
HDL (mg/dL)	1	36	55.14	13.56	0.003
	2	14	41.79	12.89	
LDL (mg/dL)	1	36	102.28	24.37	0.006
	2	14	128.86	39.70	
HbA1c (gm%)	1	36	8.68	1.20	0.251
	2	14	9.18	1.77	
Fast Bl Sugar (mg/dL)	1	36	148.75	43.75	0.476
	2	14	138.79	44.98	
Microalbuminuria	1	36	16.45	6.79	0.000
	2	14	69.29	30.95	
Visfatin (ng/ml)	1	36	12.19	6.15	0.035
	2	14	8.86	4.24	

T1DM = Type 1 Diabetes Mellitus, BMI = Body Mass Index, Ht = height, Wt = weight, HDL = high density lipoproteins, LDL = low density lipoproteins, HbA1c = glycated haemoglobin.

It also showed that there was a significant decrease in the level of visfatin in patients with microalbuminuria than in normoalbuminuric patients. It also shows that there was a highly significant increase in the incidence of occurrence of neuropathy and retinopathy in microalbuminuric than normoalbuminuric patients (Table 4).

There was a highly significant inverse relation between visfatin level with age, height, weight, BMI, waist, hip and microalbuminuria (Table5 and Figure 1).

Table 3: Comparison of demographic and anthropometric measurements in type I DM patients with normal- versus micro-albuminuria

	Normoalbuminria N = 37		Microalbuminuria N = 13		Independent t-test Chi square	
	Mean	SD	Mean	SD	t/x2	P-value
Age years	11.14	3.22	15.08	2.25	-4.060	0.0001
Male	18	48.6%	4	30.8%	1.248	0.264
Female	19	51.4%	9	69.2%		
Disease Duration [Y] Duration (years)	4.23	2.92	9.62	3.15	-5.601	0.0001
Insulin dosage dosage (I.U/kg/day)	0.95	0.23	1.13	0.25	-2.463	0.017
Ht.sds	-0.11	1.03	-0.88	0.97	2.353	0.023
Wt. sds	1.12	1.76	1.05	1.29	0.134	0.894
BMI	19.28	3.60	22.66	3.29	-2.976	0.005
Waist circumference (cm)	63.22	6.90	74.88	10.35	-4.578	0.0001
Hip circumference (cm)	76.22	12.42	91.73	13.38	-3.799	0.0001
Waist \ hip	0.84	0.05	0.82	0.05	1.003	0.321
Waist \ ht	0.45	0.03	0.49	0.05	-3.290	0.002

Ht = height, Wt = weight, BMI = Body Mass Index.

The multiple linear regression analysis using stepwise method shows that BMI is the most important predictor that affects visfatin level in the patient's group (Table 6).

Table 4: Comparison of laboratory data and presence or absence of complications in diabetic patients with normal- versus micro- albuminuria

	Norm albuminuria N=37		Microalbuminuria N=13		Independent t-test	
	Mean	SD	Mean	SD	t/x2	P-value
Triglycerides (mg/dL)	75.11	18.40	85.31	37.56	-1.284	0.205
Cholesterol (mg/dL)	170.38	25.37	189.69	40.69	-2.001	0.051
HDL (mg/dL)	55.38	13.45	40.08	11.64	3.645	0.001
LDL (mg/dL)	102.59	24.10	130.00	41.08	-2.902	0.006
HbA1c (gm%)	8.66	1.19	9.27	1.81	-1.387	0.172
Fasting blood glucose (mg/dL)	147.49	43.81	141.62	45.50	0.412	0.682
Visfatin (ng/ml)	12.20	6.07	8.59	4.29	2.444	0.015
Complications	Norm albuminuria N = 37		Microalbuminuria N = 13		Chi square test	
	No.	%	No.	%	X2	P-value
Neuropathy Negative	36	97.	6	46.2		
Positive	1	32.7	7	53.8	18.722	<0.0001
Retinopathy Negative	37	100	10	76.9	9.083	0.003
Positive	0	0.0	3	23.1		

HDL = high density lipoproteins, LDL = low density lipoproteins, HbA1c = glycated haemoglobin.

Discussion

Visfatin exerts insulin-mimetic effects that are dose dependent and quantitatively similar to those of insulin in stimulating muscle and adipocyte glucose transport and in inhibiting hepatocyte glucose production [7]. However, visfatin and insulin did not compete for binding to the insulin receptor, indicating that the two proteins were recognised by different regions of the receptor [3].

This study revealed that diabetic patients had a significantly lower visfatin level compared to the healthy controls although there was no significant difference between the two studied groups as

regarding demographic and anthropometric measures. This result comes by the previous studies done by Toruner et al. (2009), who studied circulating plasma visfatin levels in 48 adult patients with type 1 diabetes mellitus (mean age 26 ± 86 years) and found visfatin levels to be decreased in diabetic patients [4].

Table 5: Correlation between visfatin level & the studied parameters of type 1 diabetic patients group

	Visfatin			Visfatin	
	r	P-value		r	P-value
Age	-0.379**	0.007	Syst .bl.pr	-0.035	0.811
Disease Duration	-0.225	0.117	Diast.bl.pr	-0.138	0.340
Insulin Dosage	0.022	0.878	Triglycerides	-0.011	0.939
BMI	-0.418**	0.003	Cholesterol	-0.256	0.072
Waist circumference	-0.430**	0.002	HDL	0.070	0.628
Hip circumference	-0.389**	0.005	LDL	-0.203	0.158
Waist\hip ratio	0.17	0.213	HbA1c	0.120	0.408
Waist\ht ratio	-0.275	0.053	Fasting Bl Glucose	0.012	0.932
Ht.sds	0.195	0.174	Microalbuminuria	-0.323*	0.022
Wt. Sds	-0.238	0.096			

BMI = Body Mass Index, Ht = height, Wt = weight.

Similarly, Alexiadou et al. [15] study on type 1 diabetic adult patients found that fasting visfatin levels tended to be lower in patients with type 1 diabetes in comparison to healthy subjects.

Table 6: Stepwise multiple linear regression analysis for the predictors of visfatin

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
visfatin.	Constant	21.902	4.269		5.130	0.000
	BMI	-0.528	0.208	-0.344	-2.536	0.015

While another study performed on type 1 diabetic patients to study the effect of exercise on visfatin Haider et al. [6] reported increased plasma visfatin levels compared with controls in a relatively small group of adolescent patients with type 1 DM. Similarly, López-Bermejo et al. [9] reported that serum visfatin levels increase with β -cell dysfunction both in type 2 and long-standing type 1 diabetic patient. The reason of controversial data about visfatin concentrations in type 1 DM is not clear [4]. This discrepancy may, in part, be due to different study populations as our diabetic patients are younger and had a shorter duration of diabetes and higher HbA1c levels than the other study groups. Another reason could be the administration of a larger dose of exogenous insulin in our patient group as insulin can significantly suppress visfatin expression in the plasma and adipocytes [6].

In our study there was no relationship between visfatin and any of the measured values in the lipid profile, this data came corresponding with the results of the study made by Toruner et al. (2009) [4] on type 1 diabetic patients who found that visfatin concentrations did not correlate with the measured lipid parameters. Similarly, Dogru et al. [16] found no association between visfatin concentrations and lipid parameters in patients with type 2 diabetes.

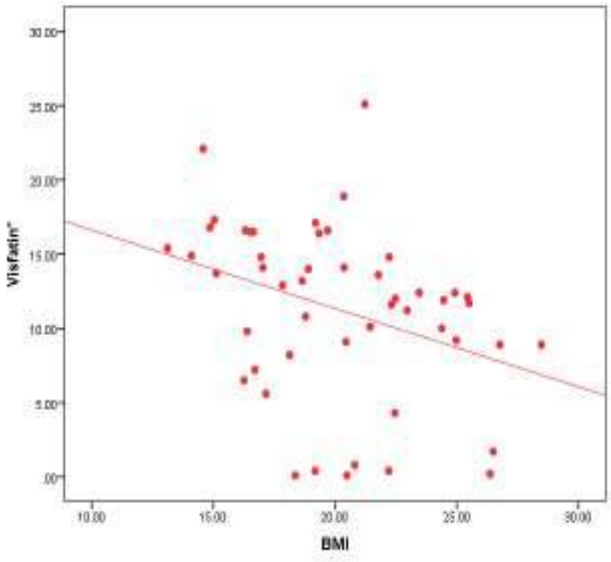

Figure 1: Correlation between visfatin level and BMI in the patients group (r = -0.418) (P = 0.003)

On the other hand, Hassan et al. [17] study indicated a significant positive correlation between visfatin level and cholesterol and VLDL-C in males and females and only with triglycerides in females and positively with LDL-C in males and negatively with HDL-C in males and females. In contrast, a negative correlation was reported between visfatin and cholesterol, triglyceride and HDL-C [18]. They suggested that visfatin may participate in cardiovascular disease and may lead to hypercholesterolemia and hypertriglyceridemia [18]. Therefore, although visfatin level is known as an adipocyte- derived peptide, there seems to be no clear relationship between circulating visfatin concentrations and lipid levels [4].

Our study showed that there was no correlation between visfatin and age in control group while there was a significant inverse correlation between visfatin 1 level with age in type 1 diabetic patients group. This result comes in agreement with the study of Jin et al. [19] who stated that fasting serum visfatin levels show significantly negative association with age. In this current study, there was no significant relationship between visfatin level and HbA1c in the studied group after adjustment for age, sex, and BMI and disease duration. This comes in correspondence with El Mesallamy et al. [20] study which stated that unexpectedly, their study did not show a correlation between visfatin levels and HbA1c %.

This study also showed a significant inverse relationship between visfatin levels and microalbuminuria after adjustment for age, sex, BMI

and disease duration. Visfatin is associated with declining glomerular filtration rate (GFR). Interestingly, glomerular mesangial cells have been shown to secrete visfatin under high glucose conditions [21], with visfatin being shown to increase angiotensinogen protein expression, which may increase renin-angiotensin system activation, which would alter GFR [22]. Whereas Kang et al. [5] study on type 2 diabetic patients with and without microalbuminuria stated that plasma visfatin levels were significantly increased in type 2 diabetic patients irrespective of the degree of microalbuminuria. Yilmaz M, et al. studied subjects with early diabetic nephropathy having microalbuminuria but no renal dysfunction and found a significant association of visfatin with proteinuria [23]. Mahmood N et al. confirmed the association of visfatin with chronic kidney disease [24].

As regarding the relationship between visfatin and duration of illness in type 1 diabetic patients, we found no significant relationship between them. Similarly, Toruner et al. (2009) found that visfatin levels were not correlated with the duration of diabetes in univariate analysis, and similar visfatin levels were observed between the patients with a short and long duration of diabetes in our study group. However, regression analysis demonstrated that the duration of diabetes was a significant predictor of circulating visfatin concentrations [4]. In this respect, López-Bermejo et al. (2006) reported no association between visfatin and duration of diabetes in adult type 1 diabetic patients with long-standing disease.

Our study found that that there was a highly significant inverse relation between visfatin level and BMI. Multiple linear regression analysis using stepwise method shows that BMI is the most important predictor to affect visfatin level in the patient's group. These results come in correspondence with Samara et al. [25] who studied visfatin gene expression and relation to BMI, they found that Visfatin expression in peripheral blood mononuclear cells (PBMCs), was significantly associated with BMI in a negative way, and these associations remained significant after separating subjects into three groups (lean, overweight, obese) for men and women. There are conflicting clinical data about the association of visfatin levels with BMI [4].

Several studies demonstrated that plasma visfatin levels correlate with obesity, visceral fat mass, type 2 diabetes and the presence of the metabolic syndrome [7, 8, 26]. Compared with lean children, obese children had significantly higher serum leptin, visfatin [27]. Other studies, however, did not confirm an association of visfatin with visceral adipose tissue or parameters of insulin sensitivity in humans and rodents [28]. Dogru et al. [29] study revealed that visfatin levels did not correlate with BMI newly diagnosed type 2 diabetics while Toruner et al. (2009) did not observe any relationship between visfatin levels and BMI. Besides, Brendt et al. [30] study showed that there is a significant relationship between visfatin concentrations and BMI and the percentage body fat in non-diabetic subjects. In disagreement with our study López-Bermejo et al. [9]; Haider et al. [6] and Alexiadous et al. [15] stated no relationship between visfatin levels and BMI in type 1 diabetic subjects.

This study has some limitations. One of these may be the lack of plasma visfatin concentrations before insulin treatment at the beginning of the diagnosis. The other is the lack of any data regarding follow-up of visfatin concentrations in type 1 diabetic patient. Further studies are required to enlighten these questions.

In conclusion, this study revealed that diabetic patients had a significantly lower visfatin level compared to the healthy controls. The study also found that there is a statistically significant decrease in the level of visfatin in patients with microalbuminuria than in normoalbuminuric patients. In this study, there was no relationship between visfatin and any of the measured values in the lipid profile. A marked decrease in the level of visfatin was shown in patients with microalbuminuria with an inverse correlation with BMI suggesting an important role of visfatin in the pathogenesis of type 1 diabetics and type 1 diabetic nephropathy.

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