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Original Article

Relation between plasma Apelin level and peripheral neuropathy in Type 2 diabetic patients

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ABSTRACT

Background: Peripheral neuropathy is one of the most common complications of both type 1 and type 2 diabetes, Long standing peripheral neuropathic pain associated with peripheral neuropathy occurs in one of six diabetic subjects, Apelin is a peptide secreted from adipocytes that seems to be beneficial in early detection of diabetic neuropathy, Itisnotedthatitincreasesindiabeticpatients and more in those with neuropathy.
Aim: We aimed to study the relation between plasma apelin levels and peripheral neuropathy in a sample of type 2 egyptian diabetic patients
Methods: The current study included 60 subjects with type 2 diabetes divided into 30 with diabetic neuropathy (group I) and 30 without diabetic neuropathy (group II) and 20 healthy subjects as a control group (group III). Fasting plasma glucose, Fasting insulin, HOMA- IR, Hemoglobin A1c, Total cholesterol, Triglycerides, High density lipoproteins, Low density lipoprotiens and Apelin levels were assessed. Neurological evaluation in diabetic subjects wasdone by nerve conduction study and clinical examination by using microfilament and tunning fork.
Results: On comparing the three studied groups a statistical significant difference in plasma Apelin levels was found ($p < 0.001$) being highest in group I followed by group II then group III(957.433 ± 221.031 pg/dl, 665.967 ± 110.991 pg/dl and 502.950 ± 201.008 pg/dl respectively). There was a statistical significant positive correlation between plasma Apelin and diabetes duration ($r = 0.5$), age ($r = 0.4$) and BMI ($r = 0.2$).
Conclusions: Apelin levels in diabetic patients are higher in the presence of neuropathy, longer disease duration, advanced age and BMI. This draws attention to the possible association between the apelinergic system and diabetic peripheral neuropathy.

1. Introduction

Type 2 Diabetes mellitus is a metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, defective insulin action or both. The chronic hyperglycemia of diabetes is associated with relatively specific long-term microvascular complications affecting the eyes, kidneys and nerves [1].

In diabetes a complex array of metabolic, vascular and perhaps hormonal factors shift the balance between nerve fiber damage and nerve fiber repair in favor of the former [2]. This occurs in a fiber selective pattern that preferentially affects distal sensory and autonomic fibers, leading to the progressive loss of sensation that underlies the clinical manifestations of diabetic neuropathy [3].

Apelin is a peptide produced and secreted by white adipose tissue, discovered in 1998 by tatemoto and other co-workers. It is synthesized as preproapelin, a protein containing 77 aminoacids which is then cleaved to shorter active fragments. As an adipokine, apelin plays a role in the regulation of many biological functions, including body energy homeostasis and glucose metabolism, water balance, and immunity [4].

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Apelin is found to be significantly higher in type 2 diabetic patients than healthy subjects. Apelin may contribute to impaired glucose metabolism by inhibiting insulin secretion. Also Apelin expression in omental fat is found to be higher than its expression in subcutaneousfat suggesting its relation to central obesity which is an important risk factor for type 2 diabetes mellitus [5].

Apelin might reflect endothelial dysfunction, microangiopathic changes and inflammation mechanisms in diabetic patients which all play some role in diabetic peripheral neuropathy (DPN) pathogenesis. Apelin might be used as a markers of DPN [6].

1.1. Aim of work

We aimed in this work is to study the relation between plasma Apelin levels and peripheral neuropathy in a sample of type 2 Egyptian diabetic patients.

1.2. Patients and methods

A case control study that included 80 subjects, 60 type 2 diabetic patients collected from the outpatient diabetes clinics of Dar El-Shefa hospital and 20 healthy subjects as a control group. It was conducted from November 2016 to march 2017. Before inclusion, an oral consent was obtained from each patient after full explanation of the study protocol. Subjects were divided into 3 groups, 30 type 2 diabetic patients with neuropathy (group I), 30 type 2 diabetic patients without neuropathy (group II) and 20 non diabetic subjects as control group (group III). Exclusion criteria included Patients with neuropathy due to other causes than diabetes, renal or hepatic disease, coronary heart disease, retinopathy, hypertensive patient on ARBS or ACEI treatment as it affect Apelin level.

Full medical history was taken from all subjects, emphasizing on the duration of diabetes mellitus, complications specially neuropathy and other co-morbid conditions. Thorough clinical examination including blood pressure measurement, weight, height, BMI (kg/m2) and neurological examination using microfilament and tunning fork was undertaken.

1.3. Laboratory studies

Laboratory tests included fasting plasma glucose (FPG), HemoglobinA1c (HbA1c), Total cholesterol (chol), Triglycerides (TG), low density lipoproteins (LDL), high density lipoproteins (HDL), fasting insulin and plasmaApelin.HbA1cwas measured by Stanbio Procedure No.0350 "Quantitative colorimetric determination of Glycohemoglobin in blood", Fasting blood glucose was measured using an automated glucose oxidase method using Behring Diagnostics Reagents (SVR Glucose Test; Behring, La Jolla, CA, USA, Lipid profile (total cholesterol, HDL, LDL, TG) by quantification colorimetric and fluorometric kit, Plasma Apelin level was measured using a double-antibody sandwich enzyme-linked immunosorbent one-step process assay (ELISA) and Fasting insulin was measured using solid phase enzyme-linked immunosorbent assay (ELISA) based on the sandwich principle (to calculate HOMA-IR ([FastingPlasmaGlucose (mg/dL) × FastingPlasmaInsulin (mIU/mL)]/405 [7].

Nerve conduction study was performed in ipsilateral upper and lower extremities. Motor and sensory conduction velocities were studied in the upper extremity segment of median and ulnar nerves. In the lower extremity segments, peroneal, posterior tibial and sural nerves were used. Nerve fibre evaluation tests reflect three conditions; Normal that means that axons and myelinatedfibers are intact, Axonal injury and axonal loss [8].

1.4. Statistical analysis

Data analysis was performed using the SPSS program (version 17, 2012, IBM Corporation, USA). Quantitative data were expressed as mean ± standard deviation (SD), whereas number and percent (%) were used for qualitative data. Independent-samples *t*-test was used when comparing two groups. One-way analysis of variance (ANOVA) was used to compare between several groups. Post-hoc test (Tukey's) was used to identify the least significant difference (LSD) among the studied groups. Pearson's correlation coefficient (r) test was used for correlating data. Mann- Whitney *U* test was used to compare quantitative variables, in non-parametric data. Stepwise multivariate regression analysis was done to define the independent predictors that affect apelin level. Probability (p-value) less than 0.05 was considered significant and less than 0.01 was considered as highly significant.

2. Results

This study was conducted on 80 subjects, they were age matched with a mean of (51.238 ± 7.784) years. We found high statistical significant difference among all studied groups regarding BMI, HbA1c, FPG, lipid profile, fasting insulin, HOMA IR and serum Apelin ($p < 0.01$).

Serum Apelinlevels were significantly increased in type 2 diabetics being higher in those with neuropathy compared to the control group (Table 1).There was a highly significant positive correlation between serum Apelin and age, duration of diabetes and BMI in all subjects ($p = 0.001$, 0.001,0.035 respectively)(Table 2). Multivariate regression analysis showed that HOMA-IR, fasting plasma glucose, fasting insulin and age are independent predictors of serum apelin levels. (Table 3).

3. Discussion

The current study showed that Apelin was significantly higher in diabetic patients and more in those with neuropathy when compared to control group. This agreed with the study of Yilmaz et al., 2016 in which Apelin levels were found to be higher in diabetic patients than healthy control. When diabetic patients were further evaluated, Apelinlevels in diabetics with peripheral neuropathy were found to be significantly higher than in those without. They supposed that elevated Apelin levels may indicate the metabolic state causing diabetic complications; it might reflect endothelial dysfunction and microangiopathic changes in diabetic patients [6]. Also this agreed with the study of Zhang et al., 2013 who found that patients with type 2 diabetes had higher apelin concentrations when compared to healthy people [9] But this finding disagreed with the study of Mehmet et al., 2009 that aimed to learn whether plasma Apelin levels were different in diabetic patients with respect to the presence of neuropathy. They observed that Apelin levels were similar in diabetic patients with and without neuropathy; however this study agreed with our study in the finding that neuropathic patients had higher Apelin levels when compared to healthy subjects [10].

This study found a highly significant positive correlation between Apelin with age and diabetic duration. This agreed with the study of Maria et al., 2012 which found a significant positive correlation between Apelin with age [11]. This disagreed with the study of Mehmet et al., 2009 which stated that in diabetic patients, plasma apelin levels were not correlated with diabetes duration and age, This may be due to the small scale of this study as it included 40 diabetic patients and 22 as a control group [10].

Also our study showed a statistical significant positive correlation between Apelin and BMI. This agreed with the study of

Table 1
: Comparison of parameters among the three studied groups.

		Subgroups			ANOVA	
		Group I	Group II	Group III	F	P-value
Age (Years)	Range	45–69	40–55	40–60	35.489	<0.001*
	Mean ± SD	58.033 ± 7.000	46.133 ± 3.812	48.700 ± 5.841		
BMI (kg/m2)	Range	28–38	28–37	28–38	9.860	<0.001*
	Mean ± SD	34.900 ± 3.144	31.667 ± 2.721	34.575 ± 3.314		
HbA1c %	Range	6–12	6.5–9.1	4.9–6.3	46.765	<0.001*
	Mean ± SD	8.633 ± 1.645	7.763 ± 0.785	5.475 ± 0.492		
Fasting plasma glucose (mg/dl)	Range	120–210	100–200	75–108	69.098	<0.001*
	Mean ± SD	169.600 ± 26.569	157.700 ± 26.914	92.450 ± 10.450		
Total cholesterol (mg/dl)	Range	187–300	178–299	176–201	6.050	0.004*
	Mean ± SD	216.333 ± 29.481	207.400 ± 26.852	191.400 ± 8.840		
LDL (mg/dl)	Range	89–170	86–176	79–110	7.518	0.001*
	Mean ± SD	122.100 ± 29.208	115.400 ± 28.011	94.500 ± 7.702		
HDL (mg/dl)	Range	35–57	35–56	40–60	10.615	<0.001*
	Mean ± SD	43.800 ± 5.455	44.600 ± 5.934	51.150 ± 6.401		
TG (mg/dl)	Range	90–201	90–201	99–150	4.103	0.020*
	Mean ± SD	146.667 ± 25.639	141.867 ± 24.324	127.800 ± 16.529		
Fasting insulin (mIu/L)	Range	19–27	19–27	17–22	18.514	<0.001*
	Mean ± SD	23.400 ± 2.724	23.233 ± 2.788	19.400 ± 1.429		
HOMA-IR	Range	6.8–14	5.43–12.4	3.46–5.7	70.632	<0.001*
	Mean ± SD	9.762 ± 1.813	9.044 ± 1.913	4.415 ± 0.573		
Apelin (pg/ml)	Range	437–1250	332–805	300–950	40.961	<0.001*
	Mean ± SD	957.433 ± 221.031	665.967 ± 110.991	502.95 ± 201.008		

Table 2
: Correlation between Apelin and other measured parameters in studied subjects.

Correlations		
Patients	Apelin (pg/ml)	
	R	P-value
Age (Years)	0.517	<0.001*
Duration of Diabetes (Years)	0.453	<0.001*
BMI (kg/m2)	0.273	0.035*
HbA1c %	0.118	0.370
Fasting blood sugar (mg/dl)	0.165	0.208
Fasting insulin (mIu/L)	0.059	0.655
HOMA-IR	0.106	0.419
Total cholesterol (mg/dl)	0.099	0.453
LDL (mg/dl)	0.106	0.420
HDL (mg/dl)	−0.145	0.269
TG (mg/dl)	0.204	0.117

Table 3
: Multivariate regression analysis between Apelin and other measured parameters.

	Unstandardized Coefficients		Standardized Coefficients	t	P-value
	B	Std. Error	Beta		
Age (Years)	15.021	7.160	0.542	2.098	0.061
Duration of Diabetes (Years)	0.761	9.735	0.022	0.078	0.938
HbA1c %	6.079	29.862	0.036	0.204	0.840
Fasting plasma glucose (mg/dl)	8.583	9.592	1.027	0.895	0.375
Fasting insulin (mIu/L)	68.615	66.312	0.825	1.035	0.306
HOMA-IR	161.817	161.286	1.340	1.003	0.321
Total cholesterol (mg/dl)	1.634	1.684	0.204	0.970	0.337
LDL (mg/dl)	1.008	1.870	0.127	0.539	0.592
HDL (mg/dl)	−3.816	5.984	−0.095	−0.638	0.527
TG (mg/dl)	1.937	1.586	0.212	1.221	0.228
BMI (kg/m2)	0.172	10.503	0.003	0.016	0.987

Xianchang et al., 2015 in which Correlation analysis showed that apelin level was positively correlated with body mass index (BMI) [12] also we were in agreement with the study of Soriguer et al. who showed that apelin levels in the morbidly obese patients were significantly higher than those of the controls when only they are diabetic [13]. But this disagreed with the study of Alaa et al., 2017 in which there was no correlation between serum Apelin and BMI in diabetic patients [14].

In our study the multivariate regression analysis found that HOMA-IR, fasting plasma glucose, fasting insulin and age are independent factors affecting the level of Apelin. This matched with the study of Li et al., 2006 in which their regression analysis showed that HOMA-IR, BMI were independent factors influencing plasma Apelinlevels [15].

4. Conclusion

In summary, the study concluded that Apelin levels were higher in itype 2 diabetic patients and a further significant increase was observed in patients with diabetic neuropathy, There is a significant positive correlation between Aplin level and longer disease duration, advanced age and BMI. Drawing attention to the possible relationship between the apelinergic system and the pathogenesis of diabetes and its complications, we believe that further studies with larger samples should be carried out, with reference to the presence of retinopathy and nephropathy as well.

Conflicts of interest

The authors declare no conflict of interests.

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LIST OF ABBREVIATIONS:

ACEI	Angiotensin converting enzyme inhibitor
ADA	American Diabetes Association
ANOVA	Analysis Of Variance
APJ	Apelin receptor
ARBS	Angiotensin II receptor blokers
BMI	Body Mass Index
CHOL	Total cholesterol
CNS	central nervous system
DPN	Diabetic peripheral neuropathy
ELISA	Enzyme-linked immunosorbent one-step process assay
FBG	Fasting Blood Glucose
FNDC5	Fibronectin Type III Domain-Containing 5
HbA1c	HemoglobinA1c
HDL	High density lipoprotein
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
LDL	Low density lipoprotein
LSD	Least Significant Difference
mRNA	messenger RNA
SD	Standard Deviation
SPSS	Statistical Package for the Social Sciences
TG	Triglycerides

References

[1] ADA. Diagnosis of diabetes mellitus. Diabetes Care 2012;35. suppl S64- S71.
[2] Callaghan BC, Cheng HT, Stables CL, et al. Diabetic neuropathy. Lancet Neurol 2012:11–521.
[3] Edwards JL, Vincent AM, Cheng HT, et al. Diabetic neuropathy management, pharmacolther diabetic neuropathy. 2008. p. 120–1.
[4] Sentinelli F, Capoccia D, Bertoccini L, et al. Genetic variant in the apelin gene. Genet Test Mol Biomarkers 2016. doi: 10.1089.
[5] Dray C, Debard C, Jager J, et al. Apelin and APJ regulation in adipose tissue and skeletal muscle of type 2 diabetic mice and humans. Am J Physiol Endocrinol Metab 2010;298:E1161–9.
[6] Yilmaz N, Bilir BI, Soysal AT, et al. Association of apelin, endoglin and endocan with diabetic peripheral neuropathy in type 2 diabetic patients. Eur Rev Med Pharmacol Sci 2016;20:892–8.
[7] Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28(7):412–9.
[8] Mark B, Bromberg. An electrodiagnostic approach to the evaluation of peripheral neuropathies. Phys Med RehabilClin N Am 2013:153–68.
[9] Zhang B-H, Wang W, Wang H, et al. Promoting effects of the adipokine, apelin, on diabetic nephropathy. PLoS One 2013;8, e60457.
[10] Mehmet GS, Hakan MT, Osman İ, et al. Plasma apelin levels in diabetic patients with and without neuropathy. J Med 2009;4(2):241–4.
[11] Maria GC, Federica S, Ilaria B. Altered glucose homeostasis is associated with increased serum apelin levels in type 2 DM. J. PLoS 2012;7(12), e51236.
[12] Xianchang S, Xingguo W, Yan Z, Xinyan Y, Wenjuan Z. Evaluation of Apelin and insulin resistance. 2015 Med SciMonit 2015;21:2547–52.
[13] Soriguer F, Garrido-Sanchez L, Garcia-Serrano S, et al. Apelin levels are increased in morbidly obese subjects with type 2 diabetes mellitus. Obes Surg 2009;19:1574–80.
[14] Alaa D, Mohamed A, Yasser G. The relationship between serum apelin level and different grades of diabetic nephropathy. Egyptian Journal of Obesity, Diabetes and Endocrinology 2017;3:32–7.
[15] Li L, Yang G, Li Q, et al. Changes and relations of circulating visfatin, apelin, and resistin levels in normal, impaired glucose tolerance, and type 2 diabetic subjects. Exp Clin Endocrinol Diabetes 2006;114:544–8.