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Evaluation of Apelin Level in Type 2 Diabetic Patients with Peripheral Neuropathy and Nephropathy

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Abstract

Background: Diabetic Peripheral Neuropathy (DPN) and Diabetic Nephropathy (DN) are serious complications of diabetes mellitus. Their pathogenesis is associated with duration of diabetes, hyperglycemia and increased pro-inflammatory response that cause endothelial dysfunction and impaired angiogenesis. Apelin is an endogenous peptide which is expressed in the kidney, adipose tissue, liver, endothelium, and plasma. It contributes to endothelial dysfunction, angiogenesis, and inflammation that lead to pathogenesis of DPN and DN.

Aim of Work: To assess serum apelin level in type 2 diabetic patients with peripheral neuropathy and nephropathy.

Patients and Methods: 80 subjects were selected from Nasser Institute for Research and divided into four groups: Group 1 included 20 healthy controls, group 2 included 20 diabetic patients without complications, group 3 included 20 patients with DPN and group 4 included 20 patients with DN. They were subjected to monofilament test, fasting blood glucose, kidney function tests, HbA1c, lipid profile, liver profile, urine analysis, urinary albumin/creatinine ratio and serum apelin.

Results: Apelin levels are significantly higher in diabetic patients in the presence of neuropathy and nephropathy compared to other groups. There was a positive correlation between serum apelin and HbA1c in group 2 and 3. Further, there was a positive correlation between apelin level and HbA1c, serum creatinine and urine albumin/creatinine ratio in group 4. There was no correlation between serum apelin and other parameters in all studied groups.

Conclusion: Serum apelin may play an important role in pathogenesis of DPN and DN.

Key Words: *Apelin – Diabetes mellitus – Diabetic nephropathy – Diabetic neuropathy.*

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Introduction

DIABETES Mellitus (DM) is a metabolic and chronic disease which is characterized by hyperglycemia and that is the major cause of micro and macrovascular complications associated with severe morbidity and mortality **[1]**.

Diabetic Peripheral Neuropathy (DPN) and Diabetic Nephropathy (DN) are common microvascular complications of diabetes. The pathogenesis of DPN is associated with duration of diabetes, hyperglycemia, pro-inflammatory response, an altered blood flow and oxidative stress. These are supposed to cause endothelial dysfunction, impaired angiogenesis, capillary basal membrane thickness and capillary thrombosis **[2,9]**. The microvascular effects of endothelial dysfunction, inflammation and angiogenesis play an important role in the development of neuronal damage **[3]**.

In early DN, there are increases in the glomerular filteration rate and glomerular filtration surface which is associated with the formation of new glomerular capillaries **[4]**. The growth of new capillaries, increased permeability of microvessls in nephrons and proliferation of glomerular endothelial cells are believed to be the main pathogenesis of DN **[5]**.

Apelin is an endogenous hormone which is synthesized as preproapelin (77 amino acids), then cleaved by angiotensin converting enzyme II to shorter active fragments (C-terminal peptides: Apelin-13, apelin-1 6, apelin-17, apelin- 19 and apelin-3 6) **[6]**.

It is widely expressed in the heart, kidney, liver, adipose tissue, gastrointestinal tract, brain, adrenal glands, endothelium, and human plasma [7,8].

Apelin plays an important role in the pathophysiology of hypertension, heart failure, cardiovascular disease, DM, and obesity [7]. Apelin contributes to the migration and proliferation of endothelial cells that result in angiogenesis and endoneurial microvascular circulation defects. Endothelial dysfunction, angiogenesis and inflammation mechanisms are responsible for the development of neuronal damage [9]. So, apelin may be used as a marker for DPN pathogenesis. Apelin mediates pathological glomerular angiogenesis by modulating the permeability in diabetic glomeruli and proliferation of glomerular endothelial cells. Therefore, apelin may play a role in the pathogenesis of DN [10].

The aim of this work is to assess serum apelin level in type 2 diabetic patients with peripheral neuropathy and nephropathy.

Patients and Methods

60 diabetic patients and 20 healthy controls were selected from Nasser Institute for Research, Cairo, Egypt, between December 2016 and November 2017. An informed consents were obtained from participants. The participants were divided into four groups: Group 1 included 20 controls; group 2 included 20 diabetic patients without complications; group 3 included 20 patients with diabetic peripheral neuropathy and group 4 included 20 patients with diabetic nephropathy. The protocol of the study was approved by the Ethical Committee of Faculty of Medicine, Menoufia University. Patients with cardiovascular diseases (coronary, carotid artery), patients with hepatic failure, malignancy, autoimmune diseases, acute or chronic infections and patients who had history of recent trauma or surgery are excluded. All participants were subjected to the following: Detailed history including demographic data, symptoms, treatment history, family history, past medical and surgical history, physical examination with assessment of Body Mass Index (BMI) and measurement of blood pressure. Also, foot examination by monofilament test was performed to detect signs of neuropathy. Further, laboratory investigations including Fasting Blood Sugar (FBS), kidney function tests, HbA1c, lipid profile, liver profile: Done by automated chemistry analyzer (Vitros 4600), urinary albumin/creatinine ratio was measured by turbidimetry, compelete urine analysis and assessment of apelin by Enzyme-Linked Immune-Sorbent Assay (ELISA). Statistical analysis was done and the data collected were tabulated and analyzed by SPSS (statistical package for social science) Version 1 8.0 on computer. Two types of statistics were done, descriptive statistics e.g. percentage (%), mean and Standard Deviation (SD) and analytic statistics e.g. Chi-square test (X^2), Student *t*-test. Pearson's correlation coefficient (*r*) test was used for correlating data. *p*-value of (<0.05) was considered statistically significant.

Results

The subjects were classified into four groups: Group 1 included 20 controls; group 2 included 20 diabetic patients without complications; group 3 included 20 patients with DPN and group 4 included 20 patients with DN.

There was no significant difference between studied groups as regard age, sex, systolic, diastolic blood pressure, blood urea, liver function (total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and albumin), total cholesterol, triglycerides, High Density Lipoproteins (HDL) and Low Density Lipoproteins (LDL). There was significant difference between all studied groups as regard BMI, presence or absence of symptoms and signs of neuropathy, fasting blood glucose and HbA1c. There was significant difference between group 4 and other studied groups regarding to serum creatinine and urinary albumin/creatinine ratio. No significant difference between other studied groups as regard serum creatinine and urinary albumin/creatinine ratio (Table 1).

There was highly significant difference between all studied groups as regard apelin level. Serum apelin was significantly higher in diabetic patients in the presence of neuropathy (group 3) and nephropathy (group 4) compared to diabetic patients without complications (group 2) and controls (Table 2).

There was a significant positive correlation between serum apelin and HbA1c in group 2 and 3. Also, there was a significant positive correlation between apelin level and HbA1c, serum creatinine and urinary albumin/creatinine ratio in group 4. No correlation could be detected between serum apelin and other parameters in studied groups (Table 3).

Table (1): Demographic data and comparisons of biochemical measurements between groups.

	Group I (controls) N=20	Group II (diabetic patients without patients) N=20	Group III (DPN patients) N=20	Group IV (DN patients) N=20	*p*-value
Age (years)	49.5±7.96	51.4±8.36	54.3±4.37	52.2±8.13	0.236
Sex:					
Male (%)	9 (45%)	9 (45%)	10 (50%)	11 (55%)	0.908
Female (%)	11 (55%)	11 (55%)	10 (50%)	9 (45%)	
BMI (kg/m^2)	25.38±1.62	29.7±2.51	28.42±3.56	28.29±3.54	0.001*
Systolic blood pressure (SBP) (mmHg)	121.75±7.48	122.75±8.35	122.5±8.96	125.5±8.09	0.502
Diastolic blood pressure (DBP) (mmHg)	75.25±4.72	75.75±5.45	78.0±6.77	78.5±5.64	0.195
Symptoms & signs of neuropathy:					
Yes (%)	0 (0%)	0 (0%)	20 (100%)	2 (10%)	0.001*
No (%)	20 (100%)	20 (100%)	0 (0%)	18 (90%)	
FBS (mg/dL)	91.65±8.41	155.95±35.68	179.5±58.16	167.75±31.93	0.001*
HbA1c (%)	5.40±0.52	6.98±0.62	9.0±0.96	7.94±0.92	0.001*
Blood Urea (mg/dL)	34.05±6.79	35.45±6.54	37.30±5.72	37.10±9.41	0.451
Serum creatinine (mg/dL)	0.86±0.25	0.90±0.22	0.92±0.24	2.60±0.98	0.001*
Total bilirubin (mg/dL)	0.90±0.26	0.84±0.18	0.84±0.18	0.86±0.21	0.826
ALT (IU/L)	43.90±14.34	49.15±10.74	43.65±13.65	50.60±8.93	0.826
AST (IU/L)	34.75±6.14	34.70±6.51	35.00±5.36	37.70±4.17	0.271
Albumin (mg/dL)	4.07±0.33	3.84±0.35	3.80±0.33	3.85±0.49	0.107
Total cholesterol (mg/dL)	261.15±67.66	249.10±66.94	239.15±51.78	246.55±30.02	0.664
Triglycerides (mg/dL)	162.25±44.40	175.75±38.87	189.35±49.04	179.85±38.46	0.257
HDL (mg/dL)	46.25±6.94	45.15±7.93	43.55±9.09	48.90±6.50	0.171
LDL (mg/dL)	174.85±93.41	163.90±68.28	162.70±48.75	176.40±47.01	0.876
Urinary albumin/creatinine ratio	16.15±4.53	23.75±4.00	28.75±5.15	390.20±196.62	0.001*
Urine analysis:					
No positive finging (%)	20 (100%)	16 (80%)	11 (55%)	17 (85%)	0.025*
Glucose (%)	0 (0%)	4 (20%)	9 (45%)	3 (15%)	

*: Highly significant.

Table (2): Comparisons between the studied groups as regard Apelin level (ng/L).

	Group I (controls) N=20	Group II (diabetic patients without complications) N=20	Group III (DPN patients) N=20	Group IV (DN patients) N=20	*p*-value
Apelin (ng/L)	71.05±16.91	135.90±17.59	195.15±27.34	250.15±51.91	0.001 *

*: Highly significant.

Table (3): Correlation between Apelin level and other parameters in all studied groups.

	Group II (diabetic patients without complications)		Group III (DPN patients)		Group IV (DN patients)	
	Apelin		Apelin		Apelin	
	r.	*p*	*r.*	*p*	*p*	*r.*
Age	0.089	0.710	–0.250	0.287	0.903	–0.029
BMI	–0.393	0.086	–0.247	0.295	0.253	–0.268
FBS	0.126	0.597	0.416	0.068	0.215	0.290
Blood urea	–0.143	0.547	0.129	0.587	0.979	0.006
Serum creatinine	0.314	0.214	0.290	0.234	0.001 *	0.671
HbA1c	0.416	0.042*	0.755	0.001 *	0.002*	0.648
Total cholesterol	0.415	0.069	0.347	0.134	0.537	–0.147
Triglycerides	0.097	0.684	0.367	0.112	0.456	–0.177
HDL	–0.371	0.107	0.139	0.560	0.435	–0.185
LDL	0.350	0.147	0.303	0.194	0.476	–0.169
Total Bilirubin	–0.255	0.278	–0.310	0.184	0.109	–0.370
ALT	0.032	0.895	–0.081	0.734	0.247	–0.272
AST	–0.065	0.785	0.280	0.245	0.856	0.043
Albumin	–0.341	0.141	–0.257	0.274	0.790	0.063
Urinary Alb/Cr	0.229	0.217	0.314	0.185	0.001 *	0.898
SBP	0.126	0.598	0.086	0.717	0.923	0.023
DBP	0.182	0.442	–0.156	0.511	0.701	–0.092

*: Highly significant.

Discussion

Diabetes Mellitus (DM) is a group of metabolic diseases in which the main finding is chronic hyperglycemia. Chronic hyperglycemia is associated with long-term damage, dysfunction, and failure of organs, especially the eyes, kidneys, nerves, heart and blood vessels **[11]**.

Apelin is an endogenous peptide hormone which is widely expressed in the kidney, heart, lung, adipose tissue, liver, endothelium, and plasma. It leads to the endothelial cell proliferation and angiogenesis **[12]**. DPN and DN are serious complications of diabetes. The pathogenesis of DPN and DN is associated with duration of diabetes, advanced age, hyperglycemia, increased pro-inflammatory response, altered blood flow and oxidative stress that are supposed to cause endothelial dysfunction and impaired angiogenesis **[2,9]**. The microvascular effects of endothelial dysfunction, inflammation and angiogenesis play an important role in the development of neuronal and kidney damage **[3]**. Therefore, apelin may play a role in pathogenesis of DPN and DN **[7,8]**.

The present study showed that apelin level was significantly higher in diabetic patients without complications group as compared to control group. This agreed with Li et al., **[13]** who found that apelin levels were significantly increased in diabetic patients and in those with impaired glucose tolerance when compared with control subjects. Therefore, there was a potential link between apelin, the pathogenesis of insulin resistance, and type 2 DM.

In agreement with that, Soriguer et al., **[14]** showed that plasma apelin concentrations in morbidly obese type 2 DM patients were significantly higher than that in controls. Also, Dray et al., **[15]** reported that plasma apelin levels increased in obese type 2 diabetic patients than control subjects.

This was supported by another study done by Zhang et al., **[10]** who observed that higher levels of apelin in patients with type 2 diabetes than control group. Habchi et al., **[7]** also found that the serum apelin level was significantly higher in type 2 diabetic patients than in controls. This could be due to the apelin/APJ system plays an important role in the pathophysiology of some diseases, including hypertension, heart failure, cardiovascular disease, DM, dyslipidemia, and obesity.

This was in agreement with Bilir et al., **[16]** who reported that apelin levels of DM patients were found to be higher than that in healthy controls. This came with Dawood et al., **[17]** who reported that the serum apelin was significantly higher in diabetic patients compared with non diabetic individuals.

However, Erdem et al., **[18]** observed that plasma apelin levels were lower in newly diagnosed and untreated type 2 diabetic patients than in healthy

controls. Also, Yavuz et al., [19] reported that there were no differences between the diabetic patients and the non diabetic ones in terms of their apelin levels. DPN patients group III was also significantly higher than control group and diabetic patients without complications group and as regard apelin level. This was in agreement with Şenol et al., [20] who reported that plasma apelin levels were found to be higher in diabetic patients with neuropathy when compared with those of control.

This was supported by subjects Bilir et al., [16] who found that apelin levels of DPN group were significantly higher than DM patients without DPN and healthy controls. This could be due to that apelin contributes to endothelial dysfunction, angiogenesis and inflammation mechanisms which all play some role in DPN pathogenesis [16].

On the other hand, Karakoc et al., [1] observed that no significant difference of apelin level was found between type 2 diabetic patients with and without complications.

Also, Şenol et al., [20] observed that apelin levels were statistically similar in diabetic patients with and without neuropathy.

Also, apelin level was significantly higher in DN patients group as compared to control group, diabetic patients without complications group and DPN patients group. This was supported by Zhang et al., [10] who observed that high apelin levels in DN patients with increase in glomerular permeability during the early stages of DN. The explanation could be that the apelin facilitates abnormal vessel formation in diabetic glomeruli, which helps DN progress. Therefore, apelin may be a crucial factor for pathological glomerular angiogenesis linked to the pathogenesis of DN.

Also, Dawood et al., [17] found that serum apelin was significantly higher in DN patients compared with diabetic patients without nephropathy and healthy controls. These results suggest that apelin may play an important role in the development of DN.

In the present study, there was significant positive correlation between apelin level and HbA 1 c in diabetic patients without complication group (GII), DPN patients group (GIII) and in DN patients group (GIV). This was agreed with Bilir et al., [16] who found that there was positive correlation between apelin level and HbA1c in DPN patients.

Dawood et al., [17] also reported that the serum apelin was significantly higher in diabetic patients compared with non diabetics and in diabetic patients (with or without nephropathy) and serum apelin had a significant direct correlation with HbA1c. This could be due to a link between apelin level and glycaemic balance in type 2 diabetic patients with states of insulin resistance. Apelin secretion is regulated by insulin, moreover, direct administration of apelin has been shown to increase insulin sensitivity, peripheral glucose uptake and decrease hyperinsulinemia. The increased apelin level observed in insulin-resistant type 2 diabetic patients, could suggest a compensatory role to reduce insulin resistance and to improve impaired insulin-secretion [21].

Also, there was significant positive correlation between apelin level and serum creatinine in DN patients (GIV). In agreement with that Dawood et al., [17] who observed that there was a significant positive correlation between serum apelin and serum creatinine in diabetic patients with nephropathy.

In this study, there was significant positive correlation between apelin level and urinary albumin/creatinine ratio in DN patients (GIV). This was supported by study done by Dawood et al., [17] who found that serum apelin was significantly higher in diabetic patients with nephropathy compared with diabetic patients without nephropathy. Moreover, it was significantly higher in patients with high-grade albuminuria compared with those with low-grade albuminuria with a significant direct correlation between serum Apelin and albumin/creatinine ration in urine.

Also, they observed a positive correlation between serum apelin and degree of DN. The explanation could be that apelin contributes to the glomerular hyperperfusion and hyperfiltration that occur in early stages of DN and modulates the permeability and proliferation of glomerular endothelial cells [10].

Conclusion:

Our study revealed that there are significantly higher apelin levels in diabetic patients with complications (peripheral neuropathy and nephropathy) as compared with diabetic patients without complications and controls.

These data suggests that apelin levels in diabetes patients are higher in the presence of neuropathy that makes attention to the possible relationship between the apelin and the pathogenesis of DPN. Also, serum apelin is significantly higher in DN patients compared with patients without nephrop-

athy. Therefore, apelin may play an important role in pathogenesis of DPN and DN and could be a novel biomarker for predicting diabetic complications. Further studies on larger number of patients should be done with reference to the presence of retinopathy.

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تقييم مستوى الآبلين فى النوع الثانى من مرضى السكرى المصابين بإعتلال العصبى الطرفى والإعتلال الكلوى

يعتبر إعتلال الآعصاب الطرفية وإعتلال الكلى من المضاعفات الآكثر خطورة فى مرض السكرى ويرتبط السبب بوجود خلل وظيفى فى خلايا بطانة الآوعية الدموية. يعد الآبلين بروتين داخلى يوجد فى كثير من الآعضاء مثل الكلى والآنسجة الدهنية والكبد وبطانة الآوعية الدموية والبلازما حيث آنه يؤدى إلى تكاثر خلايا بطانة الآوعية الدموية. لذلك، قد يلعب الآبلين دورا فى نشآة إعتلال الآعصاب الطرفية وإعتلال الكلى فى مرضى السكرى.

الهدف من الدراسة: تقييم مستوى الآبلين فى دم مرضى النوع الثانى من مرض السكرى مع وجود إعتلال الآعصاب الطرفية وإعتلال الكلى.

طرق البحث: تم إجراء هذه الدراسة فى معهد ناصر للبحوث على ستين مريض بالنوع الثانى من مرض السكرى (عشرين بدون مضعفات وعشرين مصاب بإعتلال الآعصاب الطرفية وعشرين مصاب بإعتلال الكلى) وعشرين شخص من الآصحاء وقد خضع الجميع للآتى: التاريخ المرضى الكامل، الفحص الإكلينيكى الشامل خاصة فحص القدم لتشخيص إعتلال الآعصاب الطرفية، نسبة الجلوكوز الصائم - وظائف الكلى - نسبة الهيموجلوبين السكرى - نسبة الدهون - وظائف الكبد فى الدم - تحليل البول - نسبة الآلبيومين/الكرياتينين فى البول وقياس الآبلين فى الدم بإستخدام الإليزا.

النتائج: نسبة الآبلين آعلى بكثير فى مرضى السكرى مع وجود الإعتلال العصبى وإعتلال الكلى مقارنة بالمجموعات الآخرى. هناك علاقة إيجابية بين مستوى آبلين ومستوى الهيموجلوبين السكرى فى مرضى السكرى بدون مضاعفات ومرضى إعتلال الآعصاب الطرفية. آيضا، هناك علاقة إيجابية بين مستوى الآبلين ومستوى الهيموجلوبين السكرى والكرياتينين فى الدم ونسبة الآلبيومين/الكرياتينين فى البول فى مرضى إعتلال الكلى. ولا يوجد آى إرتباط بين الآبلين والعوامل الآخرى فى الدراسة.

الإستنتاج: قد يلعب الآبلين دورا فى إعتلال الآعصاب الطرفية وإعتلال الكلى فى مرضى السكرى.

التوصيات: هناك حاجة إلى المزيد من الدراسات على عدد آكبر من المرضى مع الإشارة إلى وجود إعتلال الشبكية المصاحب لمرض السكرى.