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Plasma apelin levels in diabetic patients with and without neuropathy

Research Article

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Abstract: The aim of this study was to investigate the plasma apelin levels in diabetic patients with and without neuropathy. All consecutive diabetic patients who presented for routine follow-up at our outpatient clinic were invited to participate in this clinical study. Forty diabetic patients (20 female and 20 male) and twenty-two non-diabetic control subjects (9 female and 13 male) were included in the study. Neurological evaluations in diabetic subjects were done by nerve conduction studies and evaluated with the Neuropathy Symptom Score. Fasting plasma glucose, $HbA1_c$, lipid and apelin levels were measured in each subject. The mean plasma apelin level was significantly higher in the diabetic patients than in the control subjects ($p = 0.026$). Apelin levels were statistically similar between diabetic patients with and without neuropathy ($p = 0.43$). Further, plasma apelin levels were found to be higher in diabetic patients with neuropathy when compared with those of healthy control subjects ($p = 0.02$). In diabetic patients with neuropathy, plasma apelin levels correlated significantly with diabetes duration ($r = 0.5$, $p = 0.02$). We propose that apelin levels in diabetic patients are higher in the presence of neuropathy and longer disease duration, although this might not solely suffice as an indicator for the presence of neuropathy in diabetic patients. Drawing attention to the possible association between the apelinergic system and diabetes mellitus, we believe that further studies with larger samples should be carried out also to investigate the presence of retinopathy and nephropathy.

Keywords: *Apelin • Diabetic neuropathy • Metabolic control • Neuropathy symptom score*

1. Introduction

Apelin is a peptide-upregulated in the obese state-that displays some beneficial effects: it lowers blood pressure; modulates pituitary hormone release, food and water intake; and regulates insulin [1]. Recently, the apelinergic system has been reported to be involved in the pathogenesis of hypertension, heart failure, obesity, glucose intolerance and type 2 diabetes mellitus (DM) [2]. Plasma apelin has been found to be reduced in newly diagnosed and untreated patients with type 2 DM having no comorbidities. An imbalance in the apelinergic system might be involved in the mechanism of establishment of overt DM, as well as associated with atherosclerotic complications [3].

To the best of our knowledge, the relationship between apelin levels and diabetic polyneuropathy has not been previously reported. The aim of this study was, therefore, to investigate whether plasma apelin levels were related with neuropathy in type 2 diabetic patients.

2. Material and Methods

2.1. Patients

All consecutive diabetic patients who presented for routine follow-up at our outpatient clinic were invited to participate in this clinical study. Thirty-four patients were taking sulfonylureas, and the rest were being treated with

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diet alone. Patients who gave written informed consent underwent a complete diagnostic evaluation, including a detailed physical and neurologic examination. Nerve conduction studies (NCS) were performed and the Neuropathy Symptom Score (NSS) was recorded for all diabetic subjects. Patients with a history of peripheral nerve lesion, cervical or lumbosacral root lesion and other comorbidities like cardiovascular disease, thyroid disease, hypertension, and current infection were excluded from the study. Determination of neuropathy was based on review of the medical history, neurological tests, and conduction velocity studies described below. Forty type 2 diabetic patients (20 female and 20 male) (mean age 57.4 ± 7.9 years, body mass index (BMI): 28.4 ± 3.4 kg/m²) and twenty-two non-diabetic control subjects (13 male, 9 female) (aged 54.9 ± 6.2 years, BMI: 27.1 ± 2.6 kg/m²) were included in the study.

2.2. Biochemical analysis

Fasting plasma glucose, $HbA1_c$, and apelin levels were measured for each subject. Levels of plasma apelin were measured (Apelin 36 (Human) ELISA test kit, Catalog No: EK-057-15, Phoenix pharmaceuticals, Inc. Burlingame, CA 94010, U.S.A) by ELISA methods. This procedure was performed at the biochemical laboratory of GATA Haydarpaşa Training Hospital. Plasma glucose concentration was measured by the glucose oxidation method. Serum insulin and C-peptide levels were determined by an immuno-enzymatic method (Beckman, Immunotech, and IRMA GH). The estimate of insulin resistance by HOMA (Homeostasis Model Assessment) score was calculated using the following formula, as described by Matthews and coworkers: fasting serum insulin (μU/ml) × fasting plasma glucose (mmol/L) / 22.5 [4]. In this method, high HOMA scores denote low insulin sensitivity (insulin resistance).

2.3. Neuropathy symptom score

The neuropathy symptom score consists of 17 items, eight focusing on muscle weakness, five on sensory disturbances, and four on autonomic symptoms [5]. Items were scored as follows: negative/absent; 0, present; 1. The maximum score was 17.

2.4. Electro-diagnostic studies

After the clinical and laboratory evaluation of the patients, nerve conduction studies were performed in ipsilateral upper and lower extremities using surface electrodes with the MEDELEC™ Multimedia EMG/EP Synergy Monitoring System (London, UK). Bandpass filter settings were (Lo-fi 20 Hz, Hi-fi 3 KHz) for sensory and motor nerve studies. Motor and sensory conduction velocities were studied in the upper extremity segment of median and ulnar nerves. In the lower extremity segments, peroneal and posterior tibial nerves were used for the motor studies, and the sural nerve was used for the sensory conduction velocities. Percutaneous stimulation of the nerve was carefully performed. The extremity temperature was maintained above 31°C during the measurements, as recommended.

Response amplitudes were measured from peak to peak, and distal latencies were determined by the onset of the response. The fastest nerve fibers were used for the determination of conduction velocity.

2.5.Statistics

The statistical package SPSS (Statistical Package for Social Sciences, SPSS, Inc., Chicago, IL) for Windows 15.0 was used. χ^2 test, Pearson's correlation test, Student's *t* test and Mann-Whitney U test (if data were not normally distributed) were used. Data were presented as the mean ± SD. A *P* value < 0.05 was considered statistically significant.

3. Results

Demographic and laboratory characteristics of diabetic and healthy control subjects are summarized in Table 1. There was no statistically significant difference between the two groups in terms of age, gender, body mass index and blood pressure. We detected peripheral neuropathy in 24 (60%) of the diabetic subjects; mostly polyneuropathy (54.2%). Isolated median, ulnar or peroneal nerve involvement was present in 9, 2 and 1 patients, respectively.

Duration of diabetes was significantly higher in patients with neuropathy than in those without neuropathy (4.9 ± 3.1 vs 12.5 ± 4.0 p<0.0001). The serum fasting glucose, HbA1c, diabetes duration, and neuropathy symptom score were all statistically higher in diabetic patients with neuropathy than in those without neuropathy (Table 2).

The mean plasma apelin level was significantly higher in diabetic patients than in control subjects (p = 0.026). Apelin levels were statistically similar in diabetic patients with and without neuropathy (p = 0.43). Further, plasma apelin levels were found to be higher in diabetic patients with neuropathy when compared with those of control subjects (p = 0.02). On the other hand, that difference was not present between diabetic patients without neuropathy and healthy controls (p = 0.18). In diabetic patients, plasma apelin levels were not correlated with diabetes duration, age, HOMA-IR, BMI, total cholesterol

Table 1. Comparison of parameters in diabetic patients and the non-diabetic control group.

Parameters	Control groupn=22	Diabetic groupn=40	P value
Age (years)	54.9 ± 6.2	57.4 ± 7.9	0.18
Body mass index (kg/m^2)	27.1 ± 2.6	28.4 ± 3.4	0.11
Serum fasting glucose (mg/dl)	82.2 ± 17.9	154.0 ±5 2.4	0.0001*
HbA1c (%)	5.4 ± 0.5	7.6 ± 1.4	0.0001*
HOMA-IR	2.6 ± 2.7	5.6 ± 5.2	0.005*
Apelin (ng/ml)	1.0 ± 0.6	1.6 ± 1.4	0.026*
Total Cholesterol (mg/dl)	162.8 ± 27.8	211.2 ± 52.0	0.0001*
LDL-Cholesterol (mg/dl)	101.1 ± 27.1	135.0 ± 38.6	0,0001*
Triglyceride(mg/dl)	90.3 ± 55.2	191.6 ± 125.2	0.0001*
LDL-Cholesterol (mg/dl)	124.4 ± 37.4	142.1 ± 38.4	0,15
Triglyceride (mg/dl)	168.2 ± 132.7	206.8 ± 120.5	0.37

** Statisticaly significant*

Table 2. Comparison of parameters in diabetic patients with and without neuropathy.

Parameters	Diabetic patients without Neuropathy (n=16)	Diabetic patients with Neuropathy (n=24)	P value
Age (years)	54.6 ± 6.1	59.2 ± 8.5	0.052
Body mass index (kg/m^2)	28.2 ± 2.7	28.6± 3.8	0.73
Diabetes duration (years)	4.9 ± 3.1	12.5 ± 4.0	0.0001*
Serum fasting glucose (mg/dl)	131.9 ± 43.3	169.2± 52.4	0.019*
HbA1c (%)	6.7 ± 1.0	8.3 ± 1.3	0.0001*
HOMA-IR	5.3 ± 3.3	5.7 ± 6.2	0.78
Neuropathy Symptom Score (NSS)	1.5 ± 0.5	6.0 ± 3.3	0.0001*
Apelin (ng/ml)	1.3 ± 0.7	1.5 ± 0.8	0.43
Total Cholesterol (mg/dl)	206.6 ± 65.6	214.3 ± 41.7	0.69
LDL-Cholesterol (mg/dl)	124.4 ± 37.4	142.1 ± 38.4	0,15
Triglyceride (mg/dl)	168.2 ± 132.7	206.8 ± 120.5	0.37

** Statisticaly significant*

or triglyceride levels; whereas in diabetic patients with neuropathy, plasma apelin levels correlated significantly with diabetes duration (r = 0.5, p = 0.02).

4. Discussion

In this study, we aimed to learn whether plasma apelin levels were different in diabetic patients with respect to the presence of neuropathy. We observed that apelin levels were similar in diabetic patients with and without neuropathy; however, neuropathic patients had higher apelin levels when compared with healthy subjects.

Apelin is a recently described adipokine, plasma levels of which are markedly increased in obesity associated with insulin resistance and hyperinsulinemia [6]. The apelinergic system has also been shown to be involved in the pathogenesis of a number of high prevalence conditions such as hypertension, heart failure, HIV infections, diabetes insipidus, gastric ulcer, and osteoporosis [7].

There are only a few studies in the literature where apelin has been studied in diabetic patients. Boucher *et al.* [8] have shown that insulin exerts a direct control on apelin gene expression in adipocytes, and that, especially in obese patients, both plasma apelin and insulin levels were significantly increased. Similarly, Li *et al.* [9] have found that apelin levels were significantly increased in diabetic patients and in those with impaired glucose tolerance. Therefore, those authors have pointed out a potential link between apelin, the pathogenesis of insulin resistance, and type 2 DM. In contrast, Erdem *et al.* [3] found low plasma apelin levels in treatment-naïve patients with type 2 DM. Our results show that apelin levels were increased in diabetic patients when compared with healthy control subjects. Further, when the apelin levels were evaluated with regard to the presence of neuropathy, diabetic patients with neuropathy had significantly higher apelin levels than

the control subjects. On the other hand, since the apelin levels were found to be statistically similar in diabetic patients with and without neuropathy, we suggest that apelin level alone could not suffice as an indicator for the presence of neuropathy in diabetic patients.

Although Li *et al.* [9] have shown that plasma apelin levels were positively correlated with fasting blood glucose, HOMA-IR, BMI, and low density lipoprotein, we could not find any correlation between plasma apelin levels and some clinical/laboratory parameters with the exception of diabetes duration in patients who had neuropathy. We believe that this is in line with our previously mentioned finding that apelin levels were higher in that group of patients.

To conclude, in the light of our results, we propose that apelin levels in diabetes patients are higher in the presence of neuropathy and longer disease duration. Drawing attention to the possible relationship between the apelinergic system and the pathogenesis of diabetes, we believe that further studies with larger samples should be carried out, with reference to the presence of retinopathy and nephropathy as well.

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