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Serum apelin and ADMA levels in type 2 diabetics with and without vascular complications

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ABSTRACT

Aims: Type 2 diabetes mellitus (T2DM) is a metabolic and chronic disease which is characterized by hyperglycemia, and that is the major causes of various micro and macrovascular complications. Asymmetrical dimethylarginine (ADMA), formed by the hydrolysis of proteins containing methylated arginine residues, is an endogenous inhibitor of nitric oxide synthase (NOS), which oxidize L-arginine to citruline and nitric oxide (NO), related to hyperinsulinaemia and hyperlipidaemia. Apelin is a recently discovered peptide, present in a number of tissues and play role in insulin sensitivity improvement. In this study, our aim was to determine the levels of apelin and ADMA with glycated haemoglobin (HbA1c) in type 2 diabetic patients with or without vascular complications.
Methods: This study included (a total of) 59 diabetic patients. Of the patients, 30 were diabetic with complications, and 29 without complications. In serum samples obtained from the patients, serum ADMA and apelin levels were measured with Enzyme Linked Immunosorbent Assay (ELISA) method.
Results: Our study totally enrolled 59 patients in two groups. No significant differences were found in sex, age, HbA1c and glucose levels among groups. Apelin and ADMA levels of group with complications were lower than those of group without complications, but no statistically significant difference of apelin and ADMA levels ($p > 0.05$).
Conclusion: The results of this study have been showed no statistically significant relationship present between ADMA–apelin levels and complications of T2DM. Further studies involving larger patients populations and healthy controls should be done to clarify the pathogenetic significance of apelin and ADMA in diabetic vascular complications.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic and chronic disease which affect about 383 million adults, accounting for 8.3% of adult population. Today, prevalence and incidence of T2DM is rapidly increasing worldwide [1,2]. T2DM is characterized by hyperglycemia, and that is the major causes of various micro and macrovascular complications. The longer the duration of diabetes becomes, the more the prevalence of microvascular complications, such as nephropathy and retinopathy increases [3,4]. Vascular complications decrease the life span and the quality of life in T2DM, and it is important to prevent the development and progression of these complications [5].

Diabetes and diabetes-related complications are major causes of morbidity and mortality worldwide. Early diagnosis of the condition is important as careful diabetes management can reduce long-term vascular complications [6,7]. Long-term glycemic control is an important predictor of the micro and macrovascular complications of diabetes, but underlying mechanisms of these complications remain unclear [8]. The glycated haemoglobin (HbA1c) test has been suggested as an alternative screening test for T2DM. The measurement of HbA1c is quicker and more convenient and it is equivalent as predictors of the development of retinopathy and nephropathy [7].

Apelin is a new adipokine that is expressed and secreted from adipocytes. Insulin can up-regulate the expression of apelin in adipocytes. Apelin has been shown to regulate glucose-stimulated

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insulin secretion. Ma et al. reported that apelin is involved in glucose homeostasis [9] and it has a glucose-lowering effect. This effect was associated with enhanced glucose utilisation in skeletal muscle and adipose tissue from normal and obese insulin-resistant mice [10]. Apelin has many physiological role and the changes in plasma apelin levels have also been reported in patients with cardiometabolic disorders, including T2DM, dyslipidemia, and cardiopulmonary diseases [11,12]. Apelin may have an important role in diabetes and it could be used as a biomarker [13]. Apelin also plays a role in the regulation of the cardiovascular system, the intake of food and water and in the proliferation of cells and neovascularisation [8].

Asymmetric dimethylarginine (ADMA), an endogenous competitive nitric oxide synthase inhibitor, has also been linked to the development of diabetic microvascular complications [14]. ADMA levels are increased in several clinical conditions such as diabetes mellitus (DM), hypertension, chronic renal failure, insulin resistance syndrome, dyslipidemia, stroke, congestive heart failure, and acute coronary events [15,16]. In addition, increasing ADMA levels were associated with target organ damage including retinopathy, nephropathy, cardiac hypertrophy and cardiovascular events in patients with DM [16,17].

In this study, our aim was to determine the levels of apelin and ADMA with HbA1c in type 2 diabetic patients with or without vascular complications.

2. Material and methods

2.1. Study population

A total of 59 type 2 DM subjects who were enrolled in the Endocrinology Department of Ataturk University, Erzurum, or those with complications referred to other departments, were chosen as the study group. Informed written consent was obtained from all subjects. Patients were divided into two groups based on presence or absence of vascular complications. Group 1 consisted of 30 patients with vascular complications in T2DM, group 2 consisted of 29 patients with absence of vascular complications in T2DM. Type 2 DM was diagnosed according to the American Diabetes Association criteria [18]. Diagnosis of vascular complications in type 2 DM was based on clinical examination and laboratory investigations. Based on the clinical history, physical examination, and routine laboratory measurements, patients with such features as renal, liver and heart failure, pregnancy, steroid and nitrate usage and current smokers or smokers for the last 6 months, were excluded. The study protocol was approved by the local research ethics committee, in accordance with the declaration of Helsinki, and written informed consent forms were obtained from all participants.

2.2. Biochemical analysis

Peripheral blood samples were collected from each patient with disposable syringes through venipuncture, after an overnight fast into fluoride plus EDTA vacutainers. The blood samples were centrifuged at 3000 rpm for 10 min, to separate the plasma, which was aliquoted into microfuge tubes and immediately stored at −20 °C until analysis was done.

Glucose levels were measured in a MODULER analyser using Roche Diagnostic kits by enzymatic colorimetric method. HbA1C levels were measured by immunoturbidimetric method. Serum apelin levels were measured with Enzyme Linked Immunosorbent Assay (ELISA) using Human apelin (Phoenix Pharmaceuticals-Catalog No: EK-057-15, Lot No: 602986, INC) ELISA test kits. The apelin results were stated as pg/mL. Serum ADMA levels were measured with ELISA using Human ADMA (Immun Diagnostic – Catalog No: K7828, Lot No: 111214, Bensheim, AG) ELISA test kits. The ADMA results were stated as μmol/L.

2.3. Statistical analysis

Statistical Package for Social Sciences (SPSS) 16.0 and Sigmastat 3.1 softwares. All variables were checked for normal distribution with Shapiro–Wilk test. One-way ANOVA with post hoc Tukey test was applied for multiple comparison of normally distributed data. The normally distributed values are presented as mean ± SD. Differences were considered significant at $p < 0.05$.

3. Result

Our study totally enrolled 59 patients in two groups. No significant differences were found in sex, age, HbA1c and glucose levels among groups (Table 1). In this study, no statistically significant difference of apelin and ADMA were found between the groups with and without complications with T2DM. ADMA levels in groups with and without complications were μmol/L 0.86 ± 0.51 and 0.93 ± 0.56 ($p = 0.62$), respectively (Fig. 1). Apelin levels of group with complications were lower than those of group without complications, however this was not statistically significant (ng/mL 1.50 ± 0.41 and 1.59 ± 0.51, respectively, $p = 0.45$) (Fig. 2). Besides, there was not a correlation between ADMA and apelin levels of patients ($p = 0.47$, $r = -0.097$).

4. Discussion

T2DM with an increasing rate in worldwide, cause high rates of mortality and morbidity, besides high costs for medical treatment of the patients and workforce loss. Because patients with T2DM are at serious risk for microvascular and macrovascular complications [19]. During the past few years, much attention has been focused on the potential role of apelin and ADMA in the development of vascular complications of diabetes. This study was designed to explore the relationship between apelin and ADMA in type 2 diabetic patients with or without vascular complications.

T2DM is a state of chronic hyperglycaemia, and glycaemic control is one of the major goals of diabetes management. Several trials have shown that intensive glucose control in patients with T2DM reduces the progression of microvascular disease, but the effect on macrovascular complications remains uncertain [20,21]. Many studies show that apelin has an important role in DM and decreased circulating apelin levels in patients with newly diagnosed and untreated T2DM. Apelin plays a role in the regulation of glucose homeostasis, glucose-stimulated insulin secretion, and even insulin sensitivity [22–24]. Erdem et al. [12] show that plasma apelin levels were lower in newly diagnosed and untreated T2DM patients than in healthy control patients. Dray et al. [25] reported that plasma apelin levels increased in obese

Table 1
The demographic and clinical characteristics of groups with and without complications in T2DM patients.

	Patients with complications	Patients without complications	*p* value
N (male/female)	30(14/16)	29 (11/18)	
Age	58.4 ± 9.4	57.9 ± 12.1[a]	>0.05
HbA1c (%)	9,117 ± 1,968	9.015 ± 224[a]	>0.05
Glucose (mg/dL)	225 ± 107	222 ± 110[a]	>0.05
ADMA (μmol/L)	0.86 ± 0.51	0.93 ± 0.56[a]	>0.05
Apelin (pg/mL)	1.50 ± 0.41	1.59 ± 0.51[a]	>0.05

Data were given as mean ± SD.
[a] There were no significantly different among the groups, ($p > 0.05$).