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Is adiponectin a risk factor for transient ischaemic attacks?

Czy adiponektyna stanowi czynnik ryzyka występowania napadów przemijającego niedokrwienia mógu/przemijającego niedokrwienia mózgu?

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Abstract

Adiponectin is an adipocytokine, and it plays a role in atherosclerosis. The role of adiponectin in the development of ischaemic stroke is controversial. Up to now, adiponectin was not evaluated in transient ischaemic stroke. In this study, we investigated the relationship between adiponectin and transient ischaemic attack. Forty patients with transient ischaemic attack were included into the study. In all patients, traditional risk factors of ischaemic stroke and intima-media thickness of carotid arteries were determined. Also, the relationship between these parameters and adiponectin levels were examined. No difference was found in terms of adiponectin levels between patients and healthy subjects. In addition, there was no association between adiponectin levels and traditional risk factors. Our results suggest that adiponectin may not be a predictive risk factor of transient ischaemic attack. **(Endokrynol Pol 2015; 66 (3): 214–218)**

Key words: *adiponectin; transient ischaemic attack; intima-media thickness; atherosclerosis; lipid profile*

Streszczenie

Adiponektyna jest adipocytokiną i odgrywa ważną rolę w przebiegu miażdżycy. Jej rola w rozwoju udaru niedokrwiennego budzi kontrowersje. Aż do dziś nie oceniono działania adiponektyny w przemijających udarach niedokrwiennych. W niniejszym badaniu prześledzono związek adiponektyny z przemijającymi atakami niedokrwiennymi. Do badania włączono 40 pacjentów cierpiących na przemijające niedokrwienie mózgu. U wszystkich pacjentów wykryto typowe czynniki ryzyka udaru niedokrwiennego oraz zmiany w błonie środkowej i wewnętrznej tętnicy szyjnej. Zbadano także związek między tymi parametrami i stężeniem adiponektyny. Nie znaleziono różnic w poziomie adiponektyny między pacjentami oraz osobami zdrowymi. Dodatkowo, nie wykryto związku między stężeniem adiponektyny i typowymi czynnikami ryzyka. Wyniki badania sugerują, że adiponektyna może nie być czynnikiem ryzyka wystąpienia przemijającego ataku niedokrwiennego. **(Endokrynol Pol 2015; 66 (3): 214–218)**

Słowa kluczowe: *adiponektyna; przemijające niedokrwinie mózgu/napad przemijającego niedokrwienia mózgu; grubość błony środkowej i wewnętrznej; miażdżyca; profil lipidowy*

Introduction

Adiponectin (ADP) has recently been recognised an adipocytokine, which is accepted to have anti-inflammatory and anti-atherogenic effects. It prevents atherosclerosis by increasing nitric oxide, preventing endothelial dysfunction, and by local inhibition of inflammatory molecules [1]. Therefore, it has been thought to have a protective role in the development of ischaemic stroke. This effect has been shown in an experimental cerebral ischaemic stroke model [2]. However, clinical investigations are associated with conflicting results. This contrast may be related with the heterogeneity of ischaemic stroke [3].

Transient ischaemic attack (TIA) is defined as an acute loss of focal cerebral or ocular function with symptoms lasting < 24 hours. Previous studies measuring ADP levels were performed mainly in patients with cerebral ischaemic events but not TIA.

The aim of this study was to elucidate a predictive value of ADP in patients with TIA. We also evaluated the correlation between ADP levels and traditional stroke risks factors.

Material and methods

Study subjects

Forty patients with a diagnosis of TIA were included into the study. TIA was defined as an acute focal neurologic deficit lasting less than 24 hours. We excluded patients with TIA from a non-atherosclerotic source such as atrial fibrillation or prosthetic valves. Patients with chronic renal or hepatic failure, malignancy, recent infection, surgery, and major trauma were

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not included into the study. Twenty subjects without previous history of TIA or stroke were included into the study as a control group. Age and sex distribution was similar in both groups (p = 0.225 and 0.563, respectively). Subjects in the control group had no previous stroke.

Patients and healthy subjects were assessed according to a protocol that included demographic data, medical history, and traditional stroke risk factors. Subjects who reported daily smoking were classified as 'smokers'. Blood pressures were measured after five minutes of rest. Patients taking antihypertensive medications and/or patients with systolic/diastolic blood pressure of ≥ 140/90 mm Hg were defined as hypertensive [1, 3]. Height and weight were measured, and body mass index (BMI) was calculated as weight (in kilograms) divided by height (in metres) squared. A BMI of less than 25 was accepted as normal [4]. Waist and hip circumferences were measured and waist-to-hip ratios (WHR) were calculated. A value greater than 0.8 for a female and more than 1 for a male was accepted as abnormal [5].

In all study groups, glucose, blood haemoglobin A1c (HgA1c), insulin, C-reactive protein (CRP), blood urea nitrogen, creatinine, total cholesterol, high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), very low density lipoprotein cholesterol (VLDL), and triglyceride concentrations were measured after a minimum of 12 hours of night fasting, by routine laboratory methods. A history of diabetes mellitus (DM) and/or ≥ 126 mg/L fasting [3] plasma glucose level were defined as DM. Dyslipidaemia was defined as a total cholesterol level ≥ 200 mg/dL and/or a triglyceride level ≥ 150 mg/dL [6] and/or having received treatment for dyslipidaemia. Brain magnetic resonance imaging (MRI), and Doppler ultrasonography for carotid and vertebral arteries, were evaluated in all subjects. In Doppler ultrasonography, internal carotid artery intima-media thickness (cIMT) was measured on both sides. The measurements were made at the proximal part of the internal carotid artery, which was not seen plaque and stenosis by B mode images. The maximal cIMT was recorded at each of the vessel segments, and mean values of left and right arteries were used in the statistical analyses [7]. A cIMT of less than 1 mm was accepted as normal [8].

Analysis of ADP

Plasma samples were taken in the morning after fasting for a minimum of 12 hours. Samples drawn from an antecubital vein were quickly transferred into glass tubes and centrifuged at 3500 rpm for 5 minutes. Samples were kept at –80°C for subsequent assay. ADP serum levels were determined by ELISA (BioVendor Laboratory Medicine Inc., Brno, Czech Republic) according to the manufacturer's instructions. Both the intra- and inter-assay coefficients of variation were below 10%.

Statistical analysis

In statistical analysis the SSPE 16.00 package was used. Data were expressed as mean ± standard deviation. The normal distribution of the data was confirmed with Levene's Test for Equality of Variances. Analysis of the significance of differences between the patients and the control group was performed with the Student's t-test. Association between parameters was examined with the use of Pearson correlations. All tests were considered statistically significant at a p value < 0.05.

Results

Patient's characteristics

The clinical and laboratory findings of study probands are summarised in Table I. The rates of risk factors related with TIA are given in Table II. In the control group there were no smokers. The number of people with HT (70%, 15%), DM (27.5%, 20%), and dyslipidaemia (72.5%, 45%) in the patient group were higher than in

Table I. *Demographic, clinical, and laboratory characteristics of both groups*

Tabela I. *Cechy demograficzne, kliniczne oraz laboratoryjne obu grup*

Parameter	Patients (n:40)	Control (n:20)
	Mean ± SD	Mean ± SD
Female/male	12/28	8/12
Age (years)	64.53 ± 10.51	65.35 ± 8.33
Body mass index [kg/m^2]	26 ± 4	28 ± 4
Waist/hip ratio	0.91 ± 0.06	0.89 ± 0.06
Fasting glucose [mg/L]	101.60 ± 35.59	112.45 ± 32.47
İnsulin [mol/L]	8.10 ± 6.53	11.46 ± 4.67
Haemoglobin A1c (%)	6.28 ± 1.54	5.97 ± 1.01
Total cholesterol [mg/dL]	208.88 ± 42.28	194.55 ± 38.02
High density lipoprotein [mg/dL]	43.00 ± 14.62	43.75 ± 13.17
Low density lipoprotein [mg/dL]	134.40 ± 40.46	124.70 ± 30.08
Very low density lipoprotein [mg/dL]	32.08 ± 17.98	27.15 ± 13.23
Triglyceride [mg/dL]	158.73 ± 89.99	134.80 ± 66.27
C-reactive protein [ng/mL]	0.82 ± 1.30	0.40 ± 0.36
Blood urea nitrogen	39.35 ± 13.08	34.70 ± 10.57
Creatinine [μmol/L]	1.10 ± 0.27	0.98 ± 0.18
Carotid artery intima-media thickness [mm]	0.91 ± 0.23	0.79 ± 0.29
Adiponectin [μg/mL]	11.02 ± 8.48	9.34 ± 6.06

Table II. *Traditional risk factors in all subjects*

Tabela II. *Typowe czynniki ryzyka wśród wszystkich badanych*

Parameter	Patients n (%)		Control n (%)	
Smoking	25	62.5	0	0
Hypertension	28	70	3	15
Diabetes mellitus	11	27.5	4	20
High density lipoprotein (male < 40 female < 50)	25	62.5	12	60
Low density lipoprotein (≥ 130)	20	50	6	30
Triglyceride (≥ 150)	17	42.5	6	30
Total cholesterol (≥ 200)	25	62.5	7	35
Dyslipidaemia	29	72.5	9	45
C reactive protein (> 0.8)	11	27.5	5	25
Carotid artery intima-media thickness (≥ 1)	15	37.5	5	25
Waist-hip ratio (female ≥ 0.8 male ≥ 1)	12	30	7	35
Body mass index (≥ 25)	27	67.5	16	80

Table III. *Correlation analysis of adiponectin levels of all subjects with other parameters*

Tabela III. *Analiza korelacji stężenia adiponektyny u wszystkich badanych z innymi parametrami*

Parameter	Adiponectin	
	r	p
Sex	–0.244	0.060
Age	0.286	0.027
Body mass index	–0.060	0.647
Waist/hip ratio	–0.239	0.066
Fasting glucose	–0.006	0.961
İnsulin	–0.128	0.328
Total cholesterol	–0.092	0.486
High density lipoprotein	0.245	0.059
Low density lipoprotein	–0.112	0.395
Very low density lipoprotein	–0.192	0.142
Triglyceride	–0.212	0.104
Systolic blood pressure	–0.087	0.510
Diastolic blood pressure	–0.166	0.206
C reactive protein	–0.042	0.751
Blood urea nitrogen	–0.109	0.409
Creatinine	–0.185	0.157
Carotid artery intima-media thickness	0.221	0.090

the control group (Fig. 1). Additionally, the number of patients with increased cIMT in the patient group (37.5%) were higher than in the control group (25%). In cranial MRI, acute/subacute ischaemic lesions were determined in 13 patients. No abnormality was seen in the cranial MRIs of all subjects in the control group.

ADP levels and cerebrovascular risk factors

The mean ADP level was found as 11 μg/mL in patients group and 9.3 μg/mL in control group. No difference was found in terms of ADP levels between the groups ($p = 0.433$). The relationship between the ADP levels and other parameters is summarised in Table III. In all group analysis, no statistically significant difference was found between the ADP level and the other parameters except for age ($p = 0.027$, $r = 0.286$). There was a trend between the ADP levels and sex ($p = 0.060$, $r = –0.244$), HDL ($p = 0.059$, $r = 0.245$) and WHR ($p = 0.066$, $r = –0.239$). But these differences did not reach statistical significance.

In the patient group, no association was found between the presence of acute/subacute ischaemic lesion on MRI and ADP level ($p = 0.195$).

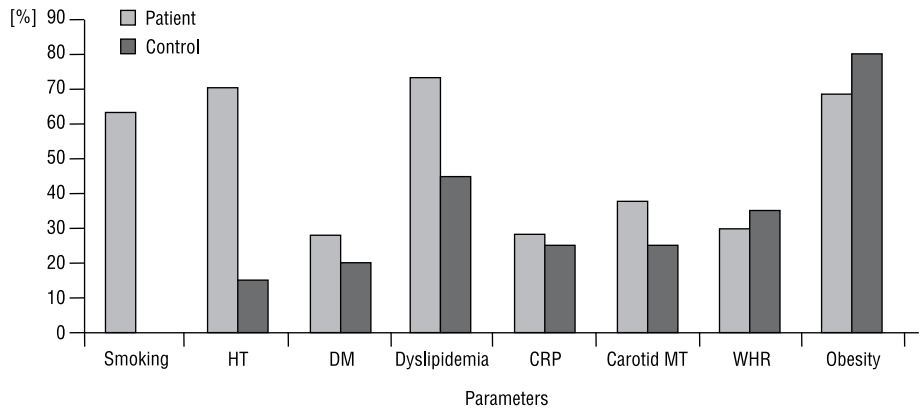

Figure 1. *The risk factors of ischaemic stroke in patients and control group*

Rycina 1. *Czynniki ryzyka udaru niedokrwiennego wśród pacjentów oraz w grupie kontrolnej*

Discussion

The role of ADP in the development of ischaemic stroke is controversial. Previously, clinical studies have found a negative [9–15], a positive [16, 17], or no association [18–22] between ischaemic stroke and ADP level. A systematic review and meta-analysis of 16 prospective studies also reported that the ADP level was not related to the risk of ischaemic stroke [23]. However, Hao et al. concluded, in a meta-analysis including 17 prospective studies, that higher ADP was associated with an increased risk of ischaemic stroke [24]. We found that the ADP level was no different in patients with TIA than in healthy persons.

Various hypotheses have been proposed to elucidate this controversial issue. One explanation for the discrepancy between studies may be a reduction of ADP clearance in renal dysfunction [16, 25]. However, we did not find a correlation between ADP levels and renal functions. Otherwise, ADP levels might change due to the influence of stroke severity and stroke subtypes. The patient groups in the studies were not homogenous in terms of stroke severity and stroke subtypes. It was reported that ADP knockout mice displayed increased cerebral infarction size [2]. Also, some clinical studies have suggested a negative correlation among ADP levels and infarct size or stroke severity [11, 20], but not others [9, 26]. In our study no difference was found in terms of ADP values between patients and control group subjects. On the other hand, sex may affect the ADP levels [23]. But we did not find a correlation between ADP and sex. Similarly, Kantarova et al. did not find an association of ADP levels with sex in acute stroke patients [12]. In addition, this conflicting result may be explained by allelic heterogeneity. Perhaps the genetic variations in the ADP gene contribute to these findings [27].

An association among ADP levels and traditional risk factor of ischaemic stroke, such as triglyceride, total cholesterol, HDL, LDL, DM, HT, and obesity, also remains unclear. In our study, ADP levels correlated positively only with age, as seen in previous studies in which ADP levels were found to be correlated with age as well as HDL and sex [15, 20, 28]. We noted a trend between the ADP levels and HDL and WHR. However, the differences did not reach statistical significance. We also investigated the association of ADP levels with cIMT. Enhanced cIMT is a marker for atherosclerosis and is predictive of future stroke. Since ADP has antiatherogenic effects, an inverse relation between cIMT and ADP levels might be expected. In fact, some authors have reported a negative correlation [7, 29]. Nonetheless, we did not find a correlation between ADP levels with cIMT. Ingleseder et al. reported a negative association of ADP levels and cIMT, whereas no relationship with the presence of atherosclerotic plaques in healthy volunteers was seen [7]. In our study, no difference was found between ADP levels and the presence of atherosclerotic plaques.

There are some weak points to our study. Firstly, we measured only the total amount of ADP. The high molecular weight ADP (HWM) is a major bioactive form with respect to endothelial function [19]. In postmenopausal women, Ogorodnikova et al. found no evidence of an association between high molecular weight adiponectin levels and ischaemic stroke [19]. Secondly, several medications may affect ADP levels [30, 31], but we could not pay attention to drug use. Another limitation of the study was the small sample size.

In conclusion, our results suggest that ADP level does not correlate with transient ischaemic stroke. We think that ADP is not a predictive risk factor of TIA. Further studies should be performed with larger sample sizes.

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