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Effects of Sympatholytic Therapy with Moxonidine on Serum Adiponectin Levels in Hypertensive Women

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We examined whether moxonidine influences lipid profile, insulin resistance, adiponectin levels, renal function and microalbuminuria in women with essential hypertension in a study of 55 non-diabetic hypertensive patients and 53 normotensive women. Hypertensive patients received moxonidine for 12 weeks. At baseline the hypertensive group had significantly higher mean blood pressure, low-density lipoprotein cholesterol, triglycerides, total cholesterol, fasting glucose, urinary albumin excretion and homeostasis model assessment of insulin resistance (HOMA-IR), together with significantly lower mean high-density lipoprotein cholesterol, creatinine clearance and serum adiponectin than the normotensive group. Moxonidine significantly decreased blood pressure, fasting glucose, triglycerides, total cholesterol, HOMA-IR and albumin excretion, but significantly increased serum adiponectin. The change in adiponectin level was negatively correlated with the change in HOMA-IR. Moxonidine treatment may improve unfavourable metabolic status related to insulin resistance by increasing adiponectin levels in patients with essential hypertension. Since it can improve adiponectin levels, it may be used in the antihypertensive treatment of patients at high risk of diabetes and cardiovascular disease.

KEY WORDS: Moxonidine; Imidazoline receptor agonists; Essential hypertension; Insulin resistance; Adiponectin

Introduction

Essential hypertension (EH) is commonly associated with insulin resistance and related disorders, such as diabetes, hyperglycaemia, hyperinsulinaemia and dyslipidaemia.[1,2] The annual incidence of diabetes in hypertensive patients who are receiving antihypertensive therapy is 2%, which increases the risk of cardiovascular disease approximately three-fold.[1,2] Antihypertensive treatment, therefore, aims to control blood pressure and prevent insulin resistance, as well as other metabolic disorders, such as dyslipidaemia and hyperglycaemia.[2,3]

Some studies suggest that the risk of developing diabetes is greater in patients receiving antihypertensive therapy with non-selective β-blockers and thiazide diuretics than in those treated with

angiotensin-converting enzyme inhibitors and angiotensin receptor blockers.[2 – 4] Although no studies show how this risk is altered when selective imidazoline receptor agonists are used to treat hypertension, experimental studies have shown that moxonidine increases insulin sensitivity and decreases hyperglycaemia and dyslipidaemia.[5 – 8] Such findings have been corroborated by clinical studies,[9,10] whereas trials investigating changes in lipid parameters of hypertensive patients treated with moxonidine have yielded contradictory results. Some studies report positive effects[10,11] whereas others find no significant effects.[12,13] In addition to these limited and confusing results, the mechanisms underlying the effects of moxonidine on insulin resistance and other related metabolic parameters are not yet clear.

Adiponectin is an adipocyte-derived cytokine of 30 kDa with antidiabetic, anti-inflammatory and anti-atherosclerotic characteristics that is believed to influence insulin sensitivity.[14,15] Studies have revealed an increase in adiponectin levels with the use of certain angiotensin receptor blockers.[16,17] There are no studies on the adiponectin levels of patients treated with selective imidazoline receptor agonists; however, the close relationship between insulin resistance and increased sympathetic activity is well known. The reason why the selective imidazoline receptor agonist moxonidine improves metabolic functions with its sympatholytic effects may, therefore, be its role in increasing adiponectin levels.

In this study we investigated whether moxonidine affects metabolic parameters, urinary albumin excretion and adiponectin levels in female patients with EH.

Patients and methods

All procedures used in the study were in accordance with the Declaration of Helsinki and approved by the Ethical Review Board of Kırıkkale University in Turkey. Prior to the study, all patients were informed about the study and they gave their consent to take part. The study was a clinical and prospective investigation conducted at the Department of Internal Medicine of the School of Medicine at Kırıkkale University during 2005 and 2006.

PATIENTS

Two groups of subjects attending outpatient clinics at the Department of Internal Medicine were included in the study: female patients with mild to moderate EH who had previously been diagnosed with EH, and normotensive (NT) females, who were matched with the EH group for body mass index (BMI). A detailed clinical history was taken from all subjects included in the study, and physical examinations, complete blood counts, routine biochemical laboratory investigations and electrocardiographic evaluations were performed. Subjects who did not smoke or drink alcohol, with no signs of diabetes mellitus, heart failure, liver disease or renal problems (excluding microalbuminuria), who did not use anti-hypertensive, antidiabetic, lipid-decreasing drugs or obesity treatment were enrolled in the study. Blood pressure was measured after a rest of 15 min in the supine position, using a standard mercury sphygmomanometer, and the mean of three measurements was taken. A diagnosis of hypertension was made for patients who had a systolic blood pressure ≥ 140 mmHg and/or a diastolic pressure ≥ 90 mmHg. The NT group consisted of subjects with blood pressure < 120/80 mmHg.

ANTIHYPERTENSIVE TREATMENT

Antihypertensive treatment was initiated in the EH group, using moxonidine in oral

tablet form at 0.4 mg/day. In order to monitor blood pressure and identify drug side-effects, patients were assessed once a week during the first month and once a month thereafter. Patients whose blood pressure could not be controlled by the lower dosage of moxonidine received an increased dose of 0.6 mg/day. Antihypertensive treatment continued for 12 weeks. Patients who could not complete the study or whose blood pressure could not be controlled by monotherapy despite the dose increase were excluded from the study.

ANTHROPOMETRIC AND BIOCHEMICAL ASSESSMENTS

Assessments performed at baseline and after 12 weeks of drug treatment included BMI, waist circumference, fasting glucose, lipid profile, creatinine, creatinine clearance, urinary albumin excretion, homeostasis model assessment of insulin resistance (HOMA-IR) index and adiponectin level. Height (cm) and weight (kg) were measured to calculate BMI as weight (kg)/height squared (m^2). Waist circumference was measured at the narrowest point above the hip.

Blood serum samples were obtained in the morning after an overnight fast of 12 – 14 h and all samples were analysed at Kırıkkale University Biochemistry Laboratories. An oral glucose tolerance test with the standard 75 g glucose load was performed in all subjects, and American Diabetes Association criteria[18] were used in order to exclude diabetes mellitus. Blood glucose, serum total and high-density lipoprotein cholesterol (HDL-cholesterol), and triglyceride levels were measured by spectrophotometric methods. Low-density lipoprotein cholesterol (LDL-cholesterol) was calculated using the Friedewald formula. Plasma insulin was measured by an electrochemiluminescence immunoassay. Serum adiponectin was determined using a validated sandwich enzyme-linked immunosorbent assay employing an adiponectin-specific antibody (catalogue no. EA2500-5, lot 4112903; Assaypro, St Charles, MO, USA).[19] The HOMA-IR index was calculated according to the formula: fasting plasma glucose concentration (mmol/l) × fasting plasma insulin concentration (μU/ml)/22.5.[20] Urinary albumin excretion (UAE) was assessed using a calorimetric method; creatinine was measured automatically with a Hitachi P800 instrument (Hitachi, Tokyo, Japan) from a 24 h urine sample and the creatinine clearance rate was calculated.

STATISTICAL ANALYSIS

Summary statistics are expressed as mean ± SD. Differences in demographic, anthropometric and metabolic characteristics between the EH and NT groups were compared by Student's *t*-test. Baseline and post-treatment data in the EH group were compared by the paired *t*-test. The relationship of basal adiponectin levels with other parameters was analysed with Pearson correlation coefficient (*r*). A value of $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS® for Windows®, version 11.5 (SPSS Inc., Chicago, IL, USA).

Results

The EH group, initially consisting of 55 patients, had a significantly higher mean blood pressure, and LDL-C, triglycerides, total cholesterol, fasting glucose and UAE levels, and significantly lower mean HDL-cholesterol and creatinine clearance than the NT group (53 subjects; Table 1) at baseline. In addition, the EH group had a higher HOMA-IR index and lower serum adiponectin levels than the NT group (Table 1). Factors correlating with HOMA-IR and

TABLE 1:
Characteristics of female normotensive (NT) subjects and female patients with essential hypertension (EH) at baseline

Characteristic	NT (n = 53)	EH (n = 55)	*P*-value
Age (years)	44.8 ± 9.6	44.7 ± 10.7	NS
BMI (kg/m^2)	30.0 ± 4.1	30.3 ± 4.7	NS
Waist circumference (cm)	95.3 ± 11.1	94.7 ± 11.7	NS
Systolic blood pressure (mmHg)	105.1 ± 12.4	156.2 ± 14.3	<0.001
Diastolic blood pressure (mmHg)	70.2 ± 10.1	95.5 ± 7.4	<0.001
HDL-cholesterol (mg/dl)	1.25 ± 0.2	1.05 ± 0.3	<0.05
LDL-cholesterol (mg/dl)	2.69 ± 0.8	3.01 ± 0.8	<0.05
Triglycerides (mg/dl)	1.97 ± 0.8	2.36 ± 1.0	<0.05
Total cholesterol (mg/dl)	4.79 ± 0.8	5.29 ± 1.0	<0.01
Creatinine (mg/dl)	0.92 ± 0.52	0.94 ± 0.33	NS
Creatinine clearance (ml/min)	92.8 ± 12.5	75.4 ± 18.0	<0.001
Urinary albumin excretion (mg/day)	15.1 ± 17.3	50.1 ± 55.0	<0.001
Fasting glucose (mg/dl)	4.24 ± 0.5	5.47 ± 0.7	<0.001
HOMA-IR index	1.80 ± 0.73	2.69 ± 1.76	=0.01
Adiponectin (µg/ml)	6.60 ± 0.70	6.27 ± 0.85	<0.05

Data shown are mean ± SD.
BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; NS not significant.

adiponectin in the EH group are shown in Table 2.

During the treatment period, two patients in the EH group were withdrawn from the study because their blood pressure could not be controlled despite increasing the dose of

TABLE 2:
Correlations (r) of study parameters with the HOMA-IR index and adiponectin levels in women with essential hypertension at baseline (n = 55)

	HOMA-IR		Adiponectin	
	r	*P*	*r*	*P*
BMI	0.326	0.001	–0.515	< 0.001
Waist circumference	0.371	<0.001	–0.528	< 0.001
Systolic blood pressure	0.373	<0.001	–0.253	< 0.01
HDL-cholesterol	–0.278	<0.01	0.220	< 0.05
Triglycerides	0.314	=0.001	–0.108	NS
Creatinine	–0.084	NS	0.522	< 0.001
Creatinine clearance	–0.068	NS	–0.548	< 0.001
Urinary albumin excretion	0.311	<0.05	–0.357	< 0.01
Fasting blood glucose	0.357	<0.001	–0.247	=0.01
HOMA-IR	–	–	–0.352	< 0.001

BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; NS not significant.

TABLE 3:
Study parameters before and after 12 weeks of moxonidine treatment in females with essential hypertension before and after 12 weeks of treatment with monoxidine in oral tablet form daily for 12 weeks at 0.4 mg/day, increasing to 0.6 mg/day if necessary to control blood pressure

	Before moxonidine (n = 51)	After moxonidine (n = 51)	Change (%)	P-value
BMI (kg/m^2)	30.7 ± 0.6	30.4 ± 0.5	–0.9 ± 16.6	NS
Waist circumference (cm)	95.4 ± 11.9	95.0 ± 10.2	–0.4 ± 14.2	NS
Systolic blood pressure (mmHg)	156.4 ± 14.1	121.8 ± 9.4	–21.5 ± 9.2	< 0.001
Diastolic blood pressure (mmHg)	95.3 ± 7.3	79.7 ± 5.8	–15.8 ± 9.0	< 0.001
HDL-cholesterol (mg/dl)	1.01 ± 0.3	1.15 ± 0.2	6.6 ± 24.2	NS
LDL-cholesterol (mg/dl)	3.02 ± 0.8	3.47 ± 1.01	0.14 ± 45.0	NS
Triglycerides (mg/dl)	2.39 ± 1.0	2.13 ± 0.8	–1.2 ± 48.0	< 0.05
Total cholesterol (mg/dl)	5.3 ± 1.2	5.0 ± 1.0	–4.7 ± 13.7	< 0.05
Creatinine (mg/dl)	0.93 ± 0.33	0.90 ± 0.27	3.7 ± 30.5	NS
Creatinine clearance (ml/min)	76.3 ± 18.2	74.0 ± 11.7	0.2 ± 18.4	NS
Urinary albumin excretion (mg/day)	53.2 ± 55.9	29.1 ± 30.1	–45.3 ± 26.7	< 0.001
Fasting blood glucose (mg/dl)	5.47 ± 0.7	5.29 ± 0.7	–2.1 ± 16.7	< 0.05
HOMA-IR	2.77 ± 1.80	2.26 ± 1.33	–11.0 ± 26.9	< 0.001
Adiponectin (µg/ml)	6.21 ± 0.85	6.63 ± 0.60	8.5 ± 16.3	= 0.01

Data shown are mean ± SD.
BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; NS not significant.

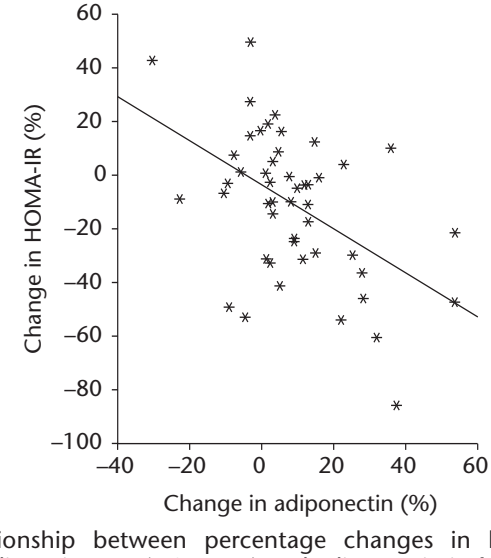

FIGURE 1: Relationship between percentage changes in homeostasis model assessment of insulin resistance (HOMA-IR) and adiponectin in females with essential hypertension before and after 12 weeks of treatment with moxonidine in oral tablet form daily for 12 weeks at 0.4 mg/day, increasing to 0.6 mg/day if necessary to control blood pressure (P < 0.001).

moxonidine to 0.6 mg/day, and two others were excluded because of loss to follow-up. During the study, no moxonidine-treated subject displayed drug side-effects that necessitated discontinuation of therapy. Moxonidine treatment significantly decreased systolic and diastolic blood pressures, triglycerides, total cholesterol, fasting blood glucose and UAE (Table 3). HOMA-IR index also significantly decreased, whereas adiponectin levels increased significantly (Table 3). The percentage change in adiponectin concentration from the baseline level was significantly negatively correlated ($r = –0.518$, $P < 0.001$) with the percentage change recorded in the HOMA-IR index (Fig. 1).

Discussion

Insulin resistance is influential in both the pathogenesis and the complications of EH.[1 – 3] In the present study, subjects with EH displayed higher insulin resistance values and more unfavourable lipid parameters, despite their lack of diabetes and the similarity of their BMI and waist circumference to the NT subjects. Another striking finding was that the women with EH had lower adiponectin levels than the NT subjects. In addition, dyslipidaemia, hyperglycaemia and increased UAE, all of which are known atherosclerotic risk factors, accompanied the lower value for adiponectin, which has a close relationship with the insulin resistance displayed by patients with EH. These findings support the view that hypo-adiponectinaemia is influential not only in diabetes mellitus and atherosclerosis, but also in the pathogenesis and complications of hypertension.[14 – 17] Although the co-occurrence of a decrease in creatinine clearance with an increase in adiponectin has been mentioned elsewhere,[21,22] it has not been satisfactorily explained. Some authors[21] have treated it as an adaptation mechanism whereas others[22] have maintained that, as a result of the decrease in creatinine clearance, the renal clearance of adiponectin may decrease and the circulating level increase.

Several experimental studies and a smaller number of clinical studies report an increase in insulin resistance with the use of moxonidine;[5 – 10] however, the mechanism leading to this is unclear. The strength of the present study is that all the subjects were women, none of them used cigarettes or alcohol, none of them was diabetic and none used antihypertensive drugs, which helped us to avoid the confounding effects of other factors. The limitation of our study is that, to analyse the results accurately and limit the study to 12 weeks, we did not employ treatment methods other than drug therapy (such as lifestyle change, exercise or dieting).

Moxonidine treatment lowered the HOMA-IR level in addition to blood pressure in the present study. We consider that the increase in insulin sensitivity in patients treated with moxonidine resulted in the improvements in serum triglycerides, total cholesterol and fasting blood glucose that were observed. Mechanisms of the effect of moxonidine on insulin sensitivity that have been reported include a direct effect on sympathetic tone, decreasing central sympathetic outflow.[23] These effects lead to increased vasodilatation and glucose uptake, an improved distribution of insulin,[23] suppression of glucagon secretion,[24] and decreased levels of norepinephrine and free fatty acids.[25] In addition, hypophagic, thermogenic and anti-obesity effects of moxonidine have been reported.[26] The present study also showed that, parallel to an improvement in insulin resistance, serum adiponectin was increased in female hypertensive patients using

moxonidine. Another mechanism leading to the positive effects of moxonidine on insulin sensitivity, serum lipids and glucose may be that the drug causes an increase in the adiponectin level by affecting small, insulin-sensitive white fat deposits at the receptor level; alternatively it may have a sympatholytic effect.

In the present study, moxonidine treatment reduced UAE by 45.3%, which has been reported in previous studies.[27,28] This may be due to the effect of moxonidine on blood pressure, indirect effects of increased insulin sensitivity or possible positive effects of an increase in adiponectin increase on the kidney. The fact that basal HOMA-IR and adiponectin values correlate significantly with basal UAE levels supports this possibility. Recent publications report that adiponectin and proteinuria levels are negatively correlated in diabetic patients[29] and that peroxisome proliferator-activated receptor-γ agonists inhibit both adiponectin increase and proteinuria.[30] However, no experimental or clinical studies using moxonidine treatment have investigated the relationship between UAE and proteinuria.

In conclusion, although patients with EH are more insulin-resistant than healthy individuals, they also display dyslipidaemia more frequently. When EH and insulin resistance occur together, dyslipidaemia and emergence of type 2 diabetes mellitus significantly increase the risk of atherosclerotic cardiovascular disease. Moxonidine treatment may improve the unfavourable metabolic status related to insulin resistance by increasing adiponectin levels, and may also reduce the risk of type 2 diabetes in patients with EH. Moxonidine may thus be used for antihypertensive treatment in hypertensive patients at high risk of diabetes and cardiovascular disease, owing to its ability to improve adiponectin levels. The present study is the first to investigate this issue and, therefore, needs to be verified in further experimental and clinical studies.

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