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The effect of perindopril and enalapril on plasma resistin levels in normotensive patients with coronary heart disease

Wpływ perindoprilu i enalaprilu na stężenie rezystyny w osoczu pacjentów z chorobą wieńcową i prawidłowym ciśnieniem tętniczym

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Abstract

Introduction: It has been suggested that adipose tissue hormones are involved in the mechanism of action of angiotensin-converting enzyme (ACE) inhibitors. Very little is known as to whether the action on resistin contributes to the clinical effectiveness associated with the use of these agents.

Material and methods: The aim of this study was to compare the effects of plasma- and tissue-type ACE inhibitors (enalapril and perindopril) on plasma resistin content in coronary artery disease (CAD) individuals without arterial hypertension. The samples used in our analysis were obtained at baseline, and again after 30 and 90 days of treatment, from 22 patients receiving enalapril (20 mg/d), 24 receiving perindopril (4 mg/d), 20 receiving no angiotensin-converting enzyme inhibitors, and 20 healthy subjects. Each group consisted of patients sensitive and resistant to insulin.

Results: Plasma resistin content was higher in normotensive CAD patients, particularly in the subgroup with reduced insulin sensitivity, than in the control group. Both ACE inhibitors produced a weak effect on blood pressure. Perindopril treatment reduced resistin levels, while enalapril only tended to decrease its content. The effect of perindopril was stronger in insulin-resistant than in insulin-sensitive subjects.

Conclusions: Our results demonstrate the superiority of perindopril over enalapril in reducing plasma resistin levels, particularly in insulin-resistant subjects. They justify the choice of a tissue-type ACE inhibitor in normotensive CAD individuals, requiring administration of this group of agents. **(Pol J Endocrinol 2010; 61 (6): 683–690)**

Key words: *perindopril, enalapril, coronary artery disease, insulin resistance, resistin*

Streszczenie

Wstęp: Hormony tkanki tłuszczowej wydają się odgrywać istotną rolę w mechanizmie działania inhibitorów enzymu konwertującego angiotensynę (ACE, *angiotensin-converting enzyme*). Bardzo niewiele wiadomo na temat związku pomiędzy wpływem na wydzielanie rezystyny a efektywnością kliniczną, związaną ze stosowaniem tej grupy leków.

Materiał i metody: Celem badania było porównanie wpływu osoczowego (enalapril) i tkankowego (perindopril) inhibitora ACE na stężenie w osoczu rezystyny u chorych z chorobą wieńcową i prawidłowym ciśnieniem tętniczym krwi. Próbki wykorzystywane w analizie pobierano przed oraz po 30 i 90 dniach leczenia od 22 osób otrzymujących enalapril (20 mg/dobę), 24 osób leczonych perindoprilem (4 mg/dobę), 20 chorych nieotrzymujących żadnego inhibitora ACE oraz od 20 zdrowych ochotników. Każda grupa obejmowała podgrupę osób z zachowaną wrażliwością na insulinę oraz podgrupę chorych z insulinoopornością.

Wyniki: W porównaniu z grupą zdrowych ochotników, osoby z chorobą wieńcową wykazywały wyższe stężenia rezystyny. Oba inhibitory ACE powodowały jedynie nieznaczne zmiany wartości ciśnienia tętniczego. Podawanie perindoprilu doprowadzało do spadku rezystynemii, podczas gdy obniżenie stężenia rezystyny w osoczu osób stosujących enalapril nie osiągało poziomu znamienności statystycznej. Wpływ perindoprilu na rezystynemię był wyraźniej wyrażony u osób z insulinoopornością.

Wnioski: Wyniki badania wskazują na silniejszy wpływ perindoprilu od enalaprilu na stężenie rezystyny w osoczu, zwłaszcza u osób z insulinoopornością. Uzyskane wyniki uzasadniają wybór tkankowego inhibitora ACE u osób z chorobą niedokrwienną, u których istnieją wskazania do zastosowania tej grupy leków. **(Endokrynol Pol 2010; 61 (6): 683–690)**

Słowa kluczowe: *perindopril, enalapril, choroba wieńcowa, insulinooporność, rezystyna*

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Introduction

Adipose tissue is a highly active metabolic and endocrine organ secreting a range of bioactive peptides with both local and distant actions [1–3]. Some of these factors, known as 'adipokines' or 'adipose tissue hormones', are specific fat-related hormones that are involved in regulating energy homeostasis, carbohydrate and lipid metabolism, and the function of the cardiovascular system [1-3]. In recent years there have been arguments that adipose tissue products are involved in the mechanism of action of angiotensin-converting enzyme (ACE) inhibitors. Administration of these agents reduced plasma leptin content in hypertensive subjects (ramipril) [4], and subjects with concomitant hypertension and obesity (enalapril) [5]. Moreover, ACE inhibitors increased plasma adiponectin levels in hypertensives (cilazapril, ramipril) [4, 6], type 2 diabetes patients (ramipril) [7], and hypertensive patients with concomitant metabolic syndrome (ramipril) [8]. Because some other studies [9–12] did not support these results, it is possible that other adipokines may be more important targets for ACE inhibitors than leptin and adiponectin.

Resistin is a member of the cysteine-rich proteins called 'resistin-like molecules' (RELM) or 'found in inflammatory zone' (FIZZ) [13]. Interestingly, there are marked interspecies differences in the source of production and structure of this protein, suggested to be a mediator of hepatic insulin resistance [13]. In mice, resistin is produced mainly by adipocytes of white adipose tissue [14]. In humans, adipocytes produce only small amounts of this protein [15], whereas relatively high levels of resistin mRNA levels are detected in stromal vascular cells of adipose tissue and in circulating mononuclear cells [16, 17]. Interestingly, mouse and human resistin share only about 64% sequence homology at the mRNA level and only 59% identity at the amino acid structure [18]. Taking into consideration the above-described differences in localisation and in amino acid structure, it is understandable that the physiological function of resistin may in part differ between humans and rodents [19]. Some [20, 21], but not all [22, 23], authors have observed that plasma resistin levels positively correlate with obesity and other components of the metabolic syndrome. Moreover, high plasma resistin levels correlate with impaired renal function in patients with chronic kidney disease [24], with the severity of inflammation in inflammatory bowel disease [25], and with increased risk for cardiac events in patients with congestive heart failure [26].

Only one study thus far has determined the action of any ACE inhibitor on resistin. Koh et al. [27] observed a ramipril-induced decrease in plasma resistin levels, although this effect was less pronounced than that of amlodipine. Interestingly, a similar beneficial action on resistinaemia was produced by angiotensin II receptor blockers (telmisartan, irbesartan) in rosiglitazone-treated type 2 diabetic subjects with metabolic syndrome [28]. Because the role of resistin in insulin sensitivity, obesity, type 2 diabetes and cardiovascular disease in humans still remains uncertain, in the present study we determined the effect of two different ACE inhibitors on plasma resistin levels in normotensive patients with coronary artery disease (CAD). Moreover, we assessed whether the presence of insulin resistance determines the strength of ACE inhibitor action.

Material and methods

Subjects

We retrospectively analysed plasma samples obtained from 66 normotensive patients with CAD included in our previous study [29]. These subjects (40–69 years old) diagnosed with CAD were enrolled in the study if they had either clinical symptoms of this disorder despite treatment with acetylsalicylic acid, a beta-blocker and a statin, or a positive result of the exercise test (defined as horizontal or downsloping ST-segment depression of at least 1 mm at 80 ms after the J point). The exclusion criteria of the original study were: 1) any form of acute coronary syndrome or a previous history of acute coronary syndrome; 2) chronic coronary artery disease being an indication for coronarography; 3) other acute ischaemic conditions (presently or in the past); 4) diabetes mellitus; 5) obesity (BMI > 30 kg/m^2); 6) symptomatic congestive heart failure; 7) any form of arterial hypertension; 8) any acute and chronic inflammatory processes; 9) impaired renal or hepatic function; 10) malabsorption syndromes; 11) previous treatment with ACE inhibitors or the existence of contraindications to administration of ACE inhibitors; and 12) poor patient compliance [29].

Study design

All individuals participating in the original study were fully informed of the purpose and the possible risks and provided written informed consent. The study was performed according to the Declaration of Helsinki, and the Ethics Committee of the Medical University of Silesia approved its protocol. They were treated for 90 days with either enalapril (20 mg daily) or perindopril (4 mg daily), or they received no ACE inhibitor. No changes in dosage during the entire study period were allowed. The samples were collected before therapy started and after 30 and 90 days of therapy. Systolic and diastolic blood pressures were measured in a sitting posture, determined during Korotkoff sounds 1 and 5, respectively. The values used in analyses were the means of

three measurements taken at intervals of at least five minutes [29].

In the present study, we chose to analyse the plasma samples of 22 subjects treated with enalapril and 24 patients treated with perindopril, as well as the samples obtained from 20 subjects receiving no ACE inhibitor (4 mg daily) and from 20 healthy individuals. On the basis of the result of HOMA index, each treatment group was divided into two subgroups, with 'normal' or 'disturbed' insulin sensitivity. Normal insulin sensitivity was arbitrarily defined as HOMA index less than 2.0. If this value was exceeded, the patient was diagnosed as insulin-resistant.

Laboratory assays

The frozen plasma samples, stored at –70°C, were thawed naturally at room temperature just before testing. All assays were carried out in duplicate, and mean values are presented.

Plasma glucose content was measured by a glucose oxidase method (Beckman, Palo Alto, CA, USA). Plasma lipids (total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides) were determined using bioMerieux reagents (Marcy-l'Etoile, France). Lipid profile was assayed by a colorimetric method (bioMerieux, France). LDL levels were measured directly. Plasma glucose levels were measured by a glucose oxidase method (Beckman, Palo Alto, CA, USA). Plasma insulin was determined with a commercial radioimmunoassay kit (Linco Research Inc, St Charles, MO, USA), that does not cross-react with proinsulin. Homeostasis model assessment (HOMA) index was calculated as the product of the fasting plasma insulin level (mU/L) and the fasting plasma glucose level (mg/dL), divided by 405. Resistin levels were investigated as previously [30] using commercially available ELISA kits (R&D Systems , Minneapolis, MN, USA). Intra- and interassay coefficients of variation of all measurements were less than 5% [30].

Statistical analysis

Results are shown as means ± standard deviation. Treatment groups were compared using one-way ANOVA followed by **Bonferroni's** post hoc analysis (arterial pressure, lipid profile and plasma glucose) or using the Kruskall-Wallis test followed by the Mann-Whitney U test (HOMA and resistin). Student's paired *t* test (arterial pressure, lipid profile and plasma glucose) or the Wilcoxon test (HOMA and resistin) were used to compare differences between the means of variables within the same treatment group. For categorical variables χ^2 test was used. Correlations were determined with Kendall's tau test. P values less than 0.05 were regarded as statistically significant. Statistical analysis was performed using the GraphPad Prism 2.01 software for Windows (GPA-26576-117).

Results

Baseline characteristics

The groups were comparable in respect of demographics, medical background, clinical characteristics and safety measurements. Compared to healthy subjects, normotensive patients with CAD had increased plasma levels of resistin ($p < 0.001$). According to our assumptions, the HOMA index was higher in insulin-resistant than in insulin-sensitive subjects ($p < 0.001$). Insulin-resistant CAD patients, when assessed together, had higher resistin levels than insulin-sensitive CAD subjects ($p < 0.05$) (Table I).

Effect of ACE inhibitors on blood pressure, insulin sensitivity and plasma lipids (data not shown)

In healthy subjects, and in CAD subjects not receiving any ACE inhibitor, blood pressure, the HOMA index and lipid profile remained unaltered throughout the study.

ACE inhibitors only insignificantly reduced systolic and diastolic blood pressure. The decrease was by 2.4/1.4 and 2.9/1.6 mm Hg (perindopril) and by 3.4/1.9 and 3.3/2.0 mmHg (enalapril), respectively, after 30 and 90 days of treatment.

Perindopril tended to reduce the HOMA index by 19.4% ($p = 0.092$) after 30 days of administration, and by 25.0% ($p < 0.05$) at the end of the study. Administered for 30 days, enalapril produced no effect on the HOMA index, but tended to reduce this parameter by 20.8% ($p = 0.078$) when given for 90 days.

Neither perindopril nor enalapril affected plasma lipids.

Effect of perindopril and enalapril on plasma resistin levels

Thirty- and 90-day treatment with perindopril reduced plasma resistin levels by, respectively, 25.8% ($p < 0.05$) and 49.2% ($p < 0.001$). Post-treatment plasma leptin did not differ from that observed in control subjects. The effect of perindopril was stronger at the end of the study than after 30 days of therapy ($p < 0.01$).

Enalapril only insignificantly reduced resistinaemia, by 20.3% ($p = 0.083$) and by 22.7% ($p = 0.056$), after 30 and 90 days of treatment, respectively. At the end of the study, plasma resistin remained higher than in healthy subjects ($p < 0.01$).

In CAD subjects not receiving any ACE inhibitor, and in healthy subjects, plasma resistin levels remained at similar levels throughout the study (Fig. 1).

Table I. *Baseline characteristics of patients*
Tabela I. *Wyjściowa charakterystyka pacjentów*

	Healthy subjects	Patients not treated with ACE inhibitor	Enalapril-treated group	Perindopril-treated group
Number of patients	20	20 (9, 11)	22 (10, 12)	24 (11, 13)
Age (years)	50.7 ± 6.4	53.1 ± 6.8 (53.5 ± 7.0, 52.8 ± 7.1)	52.9 ± 6.4 (52.4 ± 6.7, 53.3 ± 6.5)	49.2 ± 5.0 (48.2 ± 5.8, 50.1 ± 5.2)
Females	25.0	25.0 (22.2, 27.3)	22.7 (20.0, 25.0)	20.8 (18.2, 23.1)
BMI [kg/m^2]	26.4 ± 2.9	26.5 ± 2.2 (26.8 ± 2.9, 26.3 ± 2.3)	27.3 ± 2.5 (27.1 ± 2.6, 27.5 ± 2.2)	26.8 ± 2.4 (26.3 ± 2.9, 27.2 ± 2.5)
Smokers (%)	20.0	20.0 (22.2, 18.2)	18.2 (20.0, 12.5)	16.7 (18.2, 15.4)
Systolic blood pressure [mm Hg]	122.1 ± 6.0	124.6 ± 7.0 (122.3 ± 8.3, 126.5 ± 7.8)	125.5 ± 8.2 (121.6 ± 8.8, 128.8 ± 8.6)	125.8 ± 7.1 (125.0 ± 9.0, 126.5 ± 7.4)
Diastolic blood pressure [mm Hg]	78.3 ± 6.4	77.9 ± 7.5 (77.0 ± 8.2, 78.6 ± 8.0)	79.6 ± 7.1 (80.2 ± 8.5, 79.1 ± 6.9)	80.0 ± 6.2 (78.7 ± 7.3, 81.1 ± 7.0)
Medications				
Statins (%)	0	90.0*** (88.9***, 90.9***)	90.9*** (90.0***, 91.7***)	91.7*** (90.9***, 92.3***)
Acetylsalicylic acid (%)	0	85.0*** (88.9***, 81.2***)	90.9*** (90.0***, 91.7***)	91.7*** (100.0***, 84.6***)
Beta-blockers (%)	0	90.0*** (100.0***, 81.2***)	86.4*** (90.0***, 83.3***)	91.7*** (90.9***, 92.3***)
Total cholesterol [mg/dL]	167.1 ± 9.6	215.3 ± 28.3 (212.1 ± 30.1, 217.9 ± 32.0)	228.2 ± 38.2 (218.1 ± 42.4, 236.6 ± 40.0)	223.0 ± 23.1 (225.2 ± 25.2, 221.1 ± 24.0)
LDL-cholesterol [mg/dL]	91.0 ± 6.0	150.4 ± 12.1 (149.8 ± 14.0, 150.9 ± 14.1)	156.4 ± 27.5 (148.4 ± 28.5, 163.1 ± 29.8)	142.5 ± 12.3 (135.1 ± 25.2, 148.8 ± 12.3)
HDL-cholesterol [mg/dL]	51.5 ± 3.7	46.6 ± 5.0 (51.4 ± 5.6, 42.7 ± 5.1)	46.2 ± 7.9 (52.1 ± 6.2, 41.3 ± 5.9)	47.1 ± 4.8 (53.2 ± 5.7, 42.0 ± 5.6)
Triglycerides [mg/dL]	116.5 ± 23.5	143.5 ± 14.2 (124.0 ± 34.9, 159.5 ± 36.0)	149.3 ± 59.3 (121.9 ± 48.0, 172.1 ± 63.2)	143.2 ± 46.5 (121.9 ± 39.2, 161.2 ± 50.4)
Glycaemia [mg/dL]	88.0 ± 5.1	90.8 ± 5.2 (84.4 ± 5.6, 96.0 ± 5.4)	89.5 ± 9.0 (82.7 ± 4.2, 95.2 ± 5.3)	91.2 ± 8.0 (84.1 ± 8.2, 97.2 ± 8.4)
HOMA index	1.3 ± 0.2	3.7 ± 0.5** (1.4 ± 0.2, 5.5 ± 0.3******)	3.6 ± 0.5** (1.1 ± 0.2, 5.7 ± 0.2******)	3.8 ± 0.5** (1.3 ± 0.2, 6.0 ± 0.4******)
Resistin [ng/mL]	3.5 ± 0.8	6.2 ± 1.0 **** (5.6 ± 1.1, 6.7 ± 1.0***[1])	6.4 ± 1.1*** (5.8 ± 0.8, 6.9 ± 1.3***[1])	6.6 ± 1.3*** (5.7 ± 1.0, 7.3 ± 0.8***[1])

The values in parentheses represent the baseline data in subgroups with normal and reduced insulin sensitivity, respectively.
Each value represents the mean ± SD. **P < 0.01, ***P < 0.001 *v.* healthy subjects, ###P < 0.001 *v.* insulin-sensitive subjects in the same treatment group. [1]statistically different (P < 0.05) *v.* subjects with normal insulin sensitivity when all insulin-sensitive (n = 30) and all insulin-resistant (n = 36) subjects were compared to one another

The analysis of subgroups (Fig. 2)

Insulin-sensitive patients

In patients with normal value of the HOMA index, perindopril treatment insignificantly reduced plasma resistin (–22.8%, p = 0.062) after 30 days of administration and decreased it significantly by 33.3% (p < 0.01) at the end of the study. In this subgroup of subjects, no effect was produced by enalapril.

Insulin-resistant patients

Perindopril administered to insulin-resistant subjects reduced resistinaemia by 28.8% (p < 0.01) and by 58.9% (p < 0.001) after 30 and 90 days of treatment, respec-

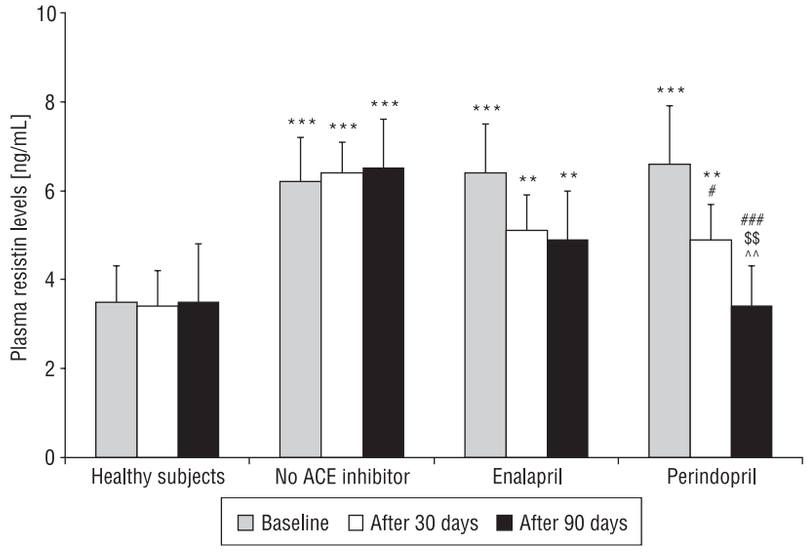

Figure 1. *Effect of angiotensin-converting enzyme inhibitors on plasma resistin levels in normotensive patients with coronary artery disease. Data represents the mean ± SD. **p < 0.01, ***p < 0.001* v. *healthy subjects, #P < 0.05, ###P < 0.001* v. *pretreatment values, $$P < 0.01 the effect stronger than after 30 days of treatment, ^^P < 0.01 the effect of perindopril stronger than that of enalapril at the end of the study*

Rycina 1. *Wpływ inhibitorów ACE na stężenie rezystyny w osoczu pacjentów z chorobą niedokrwienną serca i prawidłową wartością ciśnienia tętniczego. Wyniki przedstawiają średnią ± odchylenie standardowe. **p < 0.01, ***p < 0.001* v. *zdrowi ochotnicy; #p < 0.05, ###p < 0.001* v. *wartość przed leczeniem; $$p < 0.01 wpływ leku silniejszy niż po 30 dniach leczenia; ^^p < 0.01 pod koniec terapii wpływ perindoprilu silniejszy od enalaprilu*

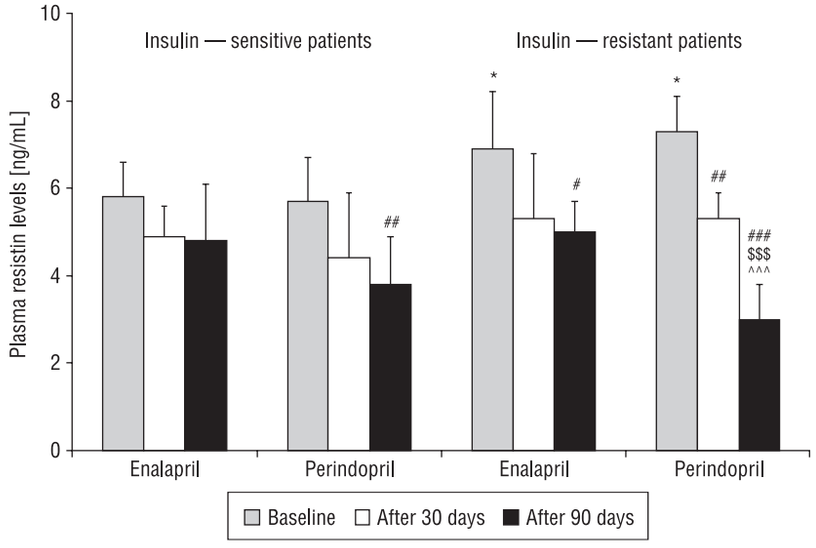

Figure 2. *The impact of angiotensin-converting enzyme inhibitors on plasma resistin levels in insulin-sensitive and insulin-resistant subjects with isolated coronary artery disease. Data represents the mean ± SD. *p < 0.05* v. *insulin-sensitive patients, #P < 0.05, ##P < 0.01, ###P < 0.001* v. *pretreatment values, $$$P < 0.001 the effect stronger than after 30 days of treatment, ^^^P < 0.001 the effect of perindopril stronger than that of enalapril at the end of the study*

Rycina 2. *Wpływ inhibitorów enzymu konwertującego angiotensynę na stężenie rezystyny w osoczu pacjentów z chorobą niedokrwienną serca i prawidłową oraz upośledzoną wrażliwością na insulinę. Wyniki przedstawiają średnią ± odchylenie standardowe. *p < 0.05 osoby z prawidłową wrażliwością na insulinę; #p < 0.05, ##P < 0.01, ###p < 0.001* v. *wartość przed leczeniem; $$$p < 0.001 wpływ leku silniejszy niż po 30 dniach leczenia; ^^^p < 0.001 pod koniec terapii wpływ perindoprilu silniejszy od enalaprilu*

tively. After 30 days of administration, enalapril tended to reduce resistin by 23.4% ($p = 0.053$), while at the end of the study this decrease was by 27.5% ($p < 0.05$).

Comparisons between the groups (Fig. 1 and 2)

Perindopril was superior to enalapril in decreasing plasma resistin levels in the whole population of normotensive subjects with CAD ($p < 0.01$) and in insulin-resistant subjects ($p < 0.001$). ACE inhibitor action on plasma resistin was more pronounced in insulin-resistant than in insulin-sensitive patients.

Correlations

At baseline, plasma resistin levels correlated with the HOMA index ($r = 0.41$, $p < 0.01$), but not with lipid profile, and systolic and diastolic blood pressure. There was a correlation between ACE inhibitor action on plasma resistin and its effect on the HOMA index ($r = 0.47$, $p < 0.01$ for perindopril; $r = 0.38$, $p < 0.05$ for enalapril). Perindopril and enalapril action on resistinaemia did not correlate with its effect on plasma lipid or arterial pressure.

Discussion

Our study found that the action of ACE inhibitors on plasma resistin is determined by pharmacokinetic and pharmacodynamic properties of these agents as well as by baseline insulin sensitivity. Normotensive CAD patients with abnormal tissue response to insulin are probably better candidates for therapy with ACE inhibitors than those with normal insulin sensitivity.

Our study revealed that individuals with CAD exhibited higher plasma resistin levels than their healthy counterparts. This finding is in line with some previous data showing that increased resistinaemia is related to increased cardiovascular risk [31, 32]. It is worth mentioning that plasma resistin slightly differed between insulin-resistant and insulin-sensitive subjects. As various responses to insulin were the only differences between the two subgroups of CAD patients, higher resistinaemia in insulin-resistant persons may suggest that the risk of the progression and development of complications is increased if CAD is accompanied by even small disturbances in insulin receptor action. Because in persons with overt diabetes insulin resistance is usually more severe than in non-diabetic individuals [33, 34], patients with concomitant CAD and type 2 diabetes probably have even higher plasma resistin content than the insulin-resistant participants in our study. If this is the case, enhanced production of resistin may contribute to the markedly increased risk of vascular complications, which is characteristic of CAD patients with type 2 diabetes [35].

Our study has shown that perindopril lowered plasma resistin levels, while the effect of enalapril was much more moderate. This finding cannot be regarded as unexpected, as it is in line with the results of the initial study [29], which showed the superiority of perindopril over enalapril in CAD patients when it comes to producing anti-inflammatory, anti-oxidant, anti-thrombotic and profibrinolytic effects. It is also in agreement with our recent, yet unpublished results [Krysiak et al. — submitted to "Polish Journal of Endocrinology"], which have shown a stronger impact of perindopril than enalapril on plasma leptin and adiponectin content in individuals with isolated CAD. The latter study, together with the present one, clearly indicate that perindopril, and possibly also other tissue-type ACE inhibitors, produce a quick, beneficial and multidirectional effect on the endocrine function of human adipose tissue. Taking into account the more pronounced anti-inflammatory, anti-oxidant and haemostatic actions of perindopril, as well as a stronger impact on peptides released by adipose tissue despite similar metabolic actions of both assessed ACE inhibitors, its seems that CAD patients requiring an ACE inhibitor should be treated with a tissue-type rather than with a plasma-type agent. Similarly as in the case of monocyte chemoattractant protein-1, interleukin-10, C-reactive protein, fibrinogen, plasminogen activator inhibitor-1 [29], leptin and adiponectin [Krysiak et al. — submitted to "Polish Journal of Endocrinology"], the resistin-lowering action of perindopril was observed despite treatment of patients with acetylsalicylic acid, a statin as well as with a β-blocker. The presence of multidirectional beneficial pleiotropic actions of perindopril in this population of patients supports their use in subjects with clinically or electrocardiographically-confirmed CAD, who experience the symptoms of this disorder despite treatment with established cardioprotective agents. These pluripotential hypotensive-independent effects may be some of the mechanisms due to which tissue ACE inhibitors are effective in the prevention of cardiovascular disorders [36, 37].

Probably the most important finding of our study is that the strength of ACE inhibitor action depended on the level of tissue insulin sensitivity. Perindopril, and to a less extent also enalapril, more effectively reduced plasma resistin in subjects with disturbed sensitivity to insulin than in those with normal tissue response to this hormone.

To the best of our knowledge, no previous study has demonstrated that the effect of any hypotensive agent on adipokines is determined by the baseline tissue sensitivity to insulin. However, it is clinically confirmed that ACE inhibitors or angiotensin II receptor blockers are effective in diabetes management, and therefore in order to prevent its complications they

should be administered to all type 2 diabetic patients, even to those without hypertension or systolic dysfunction of the left ventricle [38, 39]. The results of our study seem to broaden these indications even to subjects with milder abnormalities in insulin action. Because in this group of patients the superiority of perindopril over enalapril was particularly marked, in normotensive insulin-resistant CAD patients, tissue-type ACE inhibitors should be strongly preferred.

Although an insignificant decrease in plasma resistin in perindopril-treated subjects was observed after only 30 days of therapy, this effect was stronger at the end of the study. This suggests that perindopril should be administered for at least several months to exhibit its maximal pleiotropic effect on the hormonal function of adipose tissue, and justifies the long-term administration of these agents.

It should be mentioned that both ACE inhibitors resulted in only small changes in blood pressure. This fact, and good tolerance of perindopril and enalapril in our normotensive population, indicate that the presence of normal blood pressure cannot disqualify CAD patients from administration of an ACE inhibitor, if such a treatment is clinically justifiable.

Our study is not free from limitations. The diagnosis of CAD was established only on the basis of indirect criteria (no coronary angiography was performed). It cannot be excluded that some individuals were misdiagnosed with CAD, while some healthy subjects had asymptomatic atherosclerotic lesions in their coronary vessels. The number of patients in each group and subgroup was relatively small. Therefore, it is not unlikely that the effect of enalapril on resistinaemia is stronger than observed by us. It may reach the level of significance, provided that more participants are enrolled in the study. Nevertheless, even in such a case, the effect on plasma resistin is less pronounced than that of perindopril. Moreover, in our study the term 'insulin-resistant' encompasses subjects with impaired fasting glucose, impaired glucose tolerance and some with normal glucose tolerance (only subjects with diabetes were excluded). It is possible that ACE inhibitor action on resistin may differ between the three subgroups. Finally, as we assessed only one adipokine, the question of whether the action of ACE inhibitors on other adipose tissue products also depends on insulin sensitivity requires further investigation.

Conclusions

Our study shows that the presence of isolated CAD is associated with higher plasma levels of resistin. Perindopril exhibits a stronger resistin-lowering action than enalapril, and this effect is particularly pronounced in insulin-resistant patients. Our results indicate that tissue-type ACE inhibitors probably bring more metabolic and hormonal benefits to normotensive CAD subjects than plasma-type ones, and therefore should be preferred in this group of patients.

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