



The effect of angiotensin-converting enzyme inhibitors on plasma adipokine levels in normotensive patients with coronary artery disease

Wpływ inhibitorów konwertazy angiotensyny na stężenie adipokin w osoczu pacjentów z chorobą wieńcową i prawidłowym ciśnieniem tętniczym

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Abstract

Introduction: The results of large clinical studies indicate that angiotensin-converting enzyme (ACE) inhibitors are effective agents in patients with coronary artery disease (CAD), even if their blood pressure is within normal limits.

Material and methods: In the present study, we compared the effect of plasma- and tissue-type angiotensin-converting enzyme inhibitors on plasma levels of leptin and adiponectin in normotensive subjects with isolated CAD. We analyzed the samples obtained from 45 patients with isolated CAD, treated for 90 days with enalapril (20 mg/d, n = 15) or perindopril (4 mg/d, n = 16), or not receiving angiotensin-converting enzyme inhibitors (n = 14). Plasma leptin and adiponectin levels were determined at baseline, and after 30 and 90 days of treatment.

Results: Compared to healthy subjects (n = 15), CAD patients had lower plasma levels of adiponectin and higher plasma content of leptin. Neither enalapril nor perindopril treatment was associated with any significant changes in blood pressure. Administration of perindopril resulted in an increase in plasma adiponectin and a reduction in plasma leptin. No significant changes in these hormones were observed after enalapril treatment.

Conclusions: Our results indicate that perindopril is superior to enalapril when it comes to affecting the hormonal function of human adipose tissue. This suggests that tissue-type angiotensin-converting enzyme inhibitors are a better treatment option for normotensive individuals with CAD than plasma-type ones. (*Pol J Endocrinol* 2010; 61 (3): 280–286)

Key words: angiotensin-converting enzyme inhibitors, coronary artery disease, arterial blood pressure, leptin, adiponectin

Streszczenie

Wstęp: Wyniki dużych badań klinicznych wskazują, że inhibitory konwertazy angiotensyny (ACE, *angiotensin-converting enzyme*) są skuteczne w leczeniu pacjentów z chorobą niedokrwienną serca (CAD, *coronary artery disease*), nawet wówczas, gdy ciśnienie tętnicze jest w granicach normy.

Materiał i metody: W niniejszym badaniu porównano wpływ tkankowego i osoczkowego inhibitora ACE na stężenie w osoczu leptyny i adiponektyny u chorych z chorobą wieńcową i prawidłowym ciśnieniem tętniczym krwi. W badaniu analizowano próbki uzyskane od 45 pacjentów, którym przez 90 dni podawano enalapril (20 mg/d., n = 15), perindopril (4 mg/d., n = 16) lub u których nie stosowano żadnego inhibitora ACE (n = 14).

Wyniki: Stężenie leptyny i adiponektyny w osoczu oceniano w warunkach wyjściowych i po 30 oraz 90 dniach terapii. Wyjściowe stężenie adiponektyny było niższe, zaś leptyny wyższe niż w grupie zdrowych ochotników (n = 15). Oba oceniane leki nie wpływały znacząco na wartość ciśnienia tętniczego. Perindopril powodował wzrost adiponektynemii i spadek leptynemii. Natomiast enalapril nie powodował statystycznie znaczących zmian stężeń obu tych adipokin.

Wnioski: Uzyskane wyniki dowodzą przewagi perindoprilu nad enalaprem w zakresie wpływu na funkcję hormonalną tkanki tłuszczowej. Wskazuje to na preferencję tkankowych nad osoczkowymi inhibitorami ACE w grupie osób z chorobą wieńcową i prawidłowym ciśnieniem tętniczym. (*Endokrynol Pol* 2010; 61 (3): 280–286)

Słowa kluczowe: inhibitory konwertazy angiotensyny, choroba wieńcowa, ciśnienie tętnicze, leptyna, adiponektyna

Introduction

Angiotensin-converting enzyme (ACE) inhibitors are able to reduce cardiovascular and cerebrovascular mortality and morbidity not only in subjects with arterial

hypertension or heart failure [1]. Perindopril [2] and ramipril [3] were evidenced to decrease the frequency of cardiovascular and cerebrovascular events, fatal and non-fatal, in individuals with atherosclerosis free from systolic dysfunction of the left ventricle or heart failure



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[2, 4]. The finding that the clinical benefits of ACE inhibitors were much more strongly expressed compared with only a small reduction in blood pressure suggests that these benefits go beyond their hypotensive action [2, 4]. They may be explained by numerous pleiotropic actions being exhibited by ACE inhibitors, such as anti-inflammatory and antioxidant effects, endothelium-protective actions, antithrombotic, profibrinolytic, and anti-aggregatory effects, and regulation of muscle cell growth and migration [5–8].

An interesting target for ACE inhibitors is the hormonal function of human adipose tissue. Although various studies have determined the action of these agents on adipokine plasma levels, their results are inconsistent. Plasma leptin levels decreased after administration of ramipril to hypertensive subjects [9], after administration of enalapril to patients with concomitant hypertension and obesity [10], after treatment of Sprague-Dawley rats with perindopril [11], after administration of perindopril to rats with genetically-induced increased angiotensin II activity [12], and after treatment of normotensive adult Wistar rats with enarenal [13]. Plasma levels of adiponectin increased in hypertensive individuals treated with cilazapril [14] or ramipril [9], type 2 diabetes patients treated with ramipril [15], patients with both arterial hypertension and metabolic syndrome receiving ramipril [16], in enalapril-treated healthy male subjects exposed to a high-sodium diet [17], and in enalapril-treated spontaneously hypertensive rats [18]. However, other authors observed no changes in leptinaemia after administration of ACE inhibitors in hypertensive obese subjects [19] and in patients with essential hypertension [20]. Similarly, adiponectinaemia remained unaltered in enalapril-treated patients with essential hypertension [21] and in ramipril-treated type 2 diabetic subjects [22].

These inter-study differences in ACE inhibitor action on plasma adipokines may result from various inclusion criteria and/or different drugs used in particular studies. Unfortunately, as stated above, the studies determining ACE inhibitor action on adipose tissue products were conducted only on animals or included individuals with arterial hypertension, diabetes mellitus, and obesity. Therefore, it remains unknown whether similar effects are also observed in individuals with isolated coronary artery disease (CAD). Recently we have shown that perindopril was superior to enalapril in exhibiting anti-oxidant, anti-thrombotic, and profibrinolytic effects in CAD patients, and these actions may contribute to the clinical effectiveness of tissue ACE inhibitors in the primary and secondary prevention of cardiovascular disorders [23]. Therefore, in the present study we compared the effect on perindopril and enalapril on plasma adipokine levels in patients suffering

from CAD free from arterial hypertension, diabetes, obesity, or any form of dyslipidaemia. Both adiponectin and leptin were chosen as they belong to the best known adipose tissue products [24, 25] and their plasma levels determine the risk of CAD and its complications [26–29].

Material and methods

We retrospectively analyzed plasma samples obtained from 45 CAD patients participating in our previous study [23]. Patients (aged 42–65 years) were eligible for the study if they had stable CAD with the presence of clinical symptoms of this disorder despite treatment with acetylsalicylic acid, a β -blocker, and a statin. CAD was diagnosed on the basis of clinical symptoms and/or a positive result of an exercise test performed using a bicycle ergometer (horizontal or down-sloping ST-segment depression of at least 1 mm at 80 ms after the J point). In the original study [23], patients were excluded if they met at least one of the following criteria: 1) any form of acute coronary syndrome or a previous history of acute coronary syndromes; 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/m²); (6) symptomatic congestive heart failure; 7) any form of arterial hypertension; 8) any acute and chronic inflammatory process; 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. In the present study, we also discarded samples obtained from individuals with any form of dyslipidaemia (defined as plasma total cholesterol more than 200 mg/dL, LDL-cholesterol above 130 mg/dL and triglycerides less than 150 mg/dL).

Study design

The original study included 90 patients who, after providing written informed consent and approval the study protocol by the local bioethical committee, were allocated into one of three treatment groups. After discarding samples obtained from dyslipidaemic individuals, we analyzed samples obtained from 15 enalapril-treated subjects (20 mg daily), samples coming from 16 perindopril-treated individuals (4 mg daily), and samples from 14 subjects receiving no ACE inhibitor. The control group comprised samples obtained from 15 healthy individuals. The ACE inhibitor treatment lasted 90 days with no changes in the therapy made throughout the study. The samples had been collected before and after 30 and 90 days of therapy. During the treatment, systolic and diastolic blood pressure were monitored at each visit in a sitting position using standard cuff equip-

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	15	14	15	16
Age (years)	50.3 ± 6.5	53.2 ± 8.9	51.2 ± 6.2	48.2 ± 6.0
Females (%)	33.3	28.6	33.3	31.3
BMI [kg/m ²]	26.0 ± 3.1	26.8 ± 2.4	27.1 ± 2.3	26.4 ± 2.6
Smokers (%)	20.0	21.4	20.0	25.0
Systolic blood pressure [mm Hg]	120.1 ± 5.5	123.9 ± 6.4	124.3 ± 8.3	125.1 ± 7.4
Diastolic blood pressure [mm Hg]	77.2 ± 6.2	78.1 ± 7.1	78.8 ± 7.8	80.4 ± 6.4
Medications				
Statins (%)	0	85.7***	86.7***	93.8***
Acetylsalicylic acid (%)	0	85.7***	86.7***	87.5***
β-adrenolytics (%)	0	92.9***	93.3***	81.3***
Total cholesterol [mg/dL]	168.2 ± 10.6	171.3 ± 14.3	173.2 ± 11.2	169.4 ± 12.1
LDL-cholesterol [mg/dL]	91.3 ± 5.9	95.2 ± 5.7	98.5 ± 6.2	94.2 ± 8.6
HDL-cholesterol [mg/dL]	51.8 ± 3.5	49.5 ± 3.2	50.1 ± 3.5	51.0 ± 4.0
Triglycerides [mg/dL]	118.3 ± 14.3	120.2 ± 15.1	125.2 ± 7.8	116.0 ± 12.8
Glycaemia [mg/dL]	88.3 ± 4.2	90.5 ± 5.7	89.1 ± 6.4	88.7 ± 7.8
Leptin [ng/mL]	8.5 ± 1.1	12.9 ± 1.3***	13.2 ± 1.5***	12.8 ± 1.6***
Adiponectin [mg/L]	8.9 ± 1.1	5.6 ± 0.8***	5.3 ± 1.3***	5.2 ± 1.4***

Each value represents the mean ± SD; ***p < 0.001 v. healthy subjects

ment. They were determined during Korotkoff sounds 1 and 5. The values used in statistical analyses were the means of 3 measurements taken at intervals of at least 5 min, starting 15 min after the patient had sat down.

Laboratory assays

The plasma samples, stored at -70°C, were thawed at room temperature just before analysis. To minimize analytical errors, all measurements were performed in duplicate.

Plasma glucose content was measured using a glucose oxidase method (Beckman, Palo Alto, USA). Plasma lipids (total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides) were determined by a colorimetric method using bioMerieux reagents (Marcy-l'Etoile, France).

Leptin and adiponectin levels were estimated using commercially available ELISA kits obtained from R&D Systems (McKinley Place N.E. Minneapolis, USA) according to the manufacturer's instructions. Intra- and interassay coefficients of variation of all measurements were as described previously [30].

Statistical analysis

Results are presented as means ± SD. Comparisons between the groups were performed using one-way ANOVA followed by post hoc Bonferroni test (arterial pressure, lipid profile, and plasma glucose) or using the Kruskal-

Wallis test followed by the Mann-Whitney U test (leptin and adiponectin). Pre-, inter-, and post-treatment results within the same treatment group were compared with either Student's paired t test (arterial pressure, lipid profile, and plasma glucose) or the Wilcoxon test (leptin and adiponectin). For categorical variables, the χ^2 test was used. Correlations were assessed using Kendall's tau test. Values of p < 0.05 were considered statistically significant. Statistical analysis was carried out using GraphPad Prism 2.01 software for Windows (GPA-26576-117).

Results

Baseline characteristics (Table I)

The groups treated with perindopril, those treated with enalapril, and those not receiving ACE inhibitors were comparable in terms of sex, weight, age, medical background, clinical characteristics, and other demographic data. Most CAD patients were treated with statins, β-adrenolytics, and acetylsalicylic acid, with no differences between the treatment groups. Patients with CAD exhibited higher plasma leptin levels and lower plasma adiponectin content.

Effect of ACE inhibitors on blood pressure

Both perindopril and enalapril only tended to reduce blood pressure by 2.2/1.3 and 2.8/1.5 mm Hg (perin-

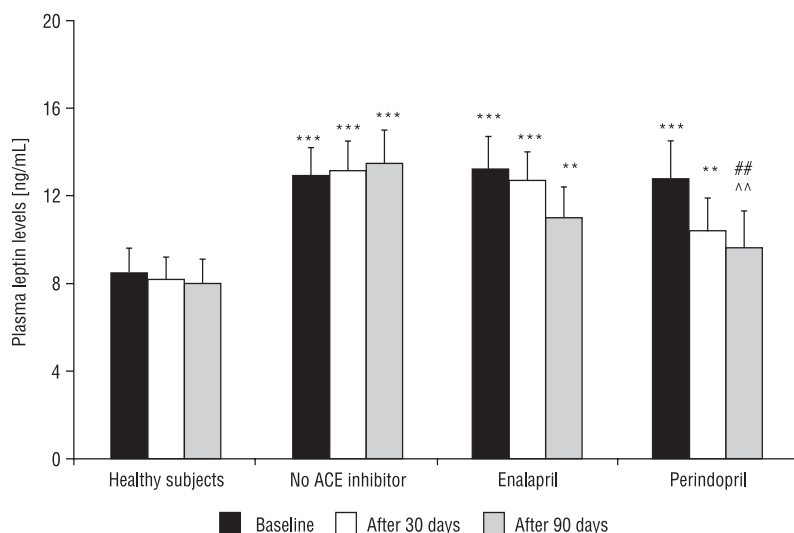


Figure 1. Effect of angiotensin-converting enzyme inhibitors on plasma leptin levels in normotensive patients with coronary artery disease. Data represent the mean \pm SD; ** $p < 0.01$, *** $p < 0.001$ v. healthy subjects; ## $p < 0.01$ v. pretreatment values; ^ $p < 0.01$ the effect of perindopril stronger than that of enalapril at the end of the study

Rycina 1. Wpływ inhibitorów enzymu konwertazy angiotensyny na stężenie leptyny w osoczu pacjentów z chorobą niedokrwienną serca i prawidłową wartością ciśnienia tętniczego. Wyniki przedstawiają średnią \pm odchylenie standardowe; ** $p < 0,01$, *** $p < 0,001$ v. zdrowi ochotnicy; ## $p < 0,01$ v. wartość przed leczeniem; ^ $p < 0,01$ pod koniec terapii wpływ perindoprilu silniejszy od enalaprilu

dopril) and by 3.5/2.0 and 3.0/1.7 mm Hg (enalapril) after 30 and 90 days of treatment, respectively. No changes in blood pressure were observed in the remaining groups of patients (data not shown).

Effect of ACE inhibitors on plasma adipokine levels

Leptin (Fig. 1)

Administered for 30 days, perindopril tended to reduce plasma leptin levels (by 18.8%, $p = 0.075$). After 90 days, perindopril decreased plasma levels of this protein by 25.0% ($p < 0.01$). At the end of the study, plasma levels of leptin in CAD patients did not differ from those observed in healthy subjects.

Thirty-day management with enalapril did not affect plasma leptin, while at the end of the treatment period the drug induced an insignificant decrease of leptinaemia (by 16.7%, $p = 0.082$). After 90 days of enalapril administration, plasma leptin levels still exceeded those observed in the control group.

In normotensive individuals with CAD who were not treated with ACE inhibitors, plasma leptin levels remained unaltered throughout the study.

Adiponectin (Fig. 2)

Perindopril increased plasma adiponectin levels by 23.1% ($p < 0.05$) and by 61.5% ($p < 0.001$) after 30 and 90 days of treatment, respectively. A perindopril-in-

duced increase in adiponectinaemia was stronger after 90 days than after 30 days of treatment ($p < 0.01$). At the end of the study, plasma adiponectin content in CAD patients did not differ from those observed in healthy subjects.

Enalapril only insignificantly increased adiponectin levels. After 30 days this reduction was 18.9% ($p = 0.069$), while at the end of the study it was 20.8% ($p = 0.056$). At the end of the study, plasma adiponectin levels were still higher than in the control group.

No changes in plasma adiponectin content were observed in CAD patients who were not given any ACE inhibitor.

Comparisons between the groups (Fig. 1 and 2)

Perindopril was superior to enalapril in reducing plasma leptin levels ($p < 0.01$) and increasing plasma adiponectin ($p < 0.001$).

Correlations

At entry, plasma content of leptin correlated weakly with both systolic ($r = 0.32$, $p < 0.05$) and diastolic ($r = 0.35$, $p < 0.01$) blood pressure. There was an inverse correlation between plasma adiponectin and systolic ($r = -0.38$, $p < 0.01$) and diastolic ($r = -0.31$, $p < 0.05$) blood pressure. No correlation was observed between perindopril and enalapril action on plasma adipokine levels and the effects of these agents on systolic and diastolic arterial pressure, plasma glucose, and lipid profile.

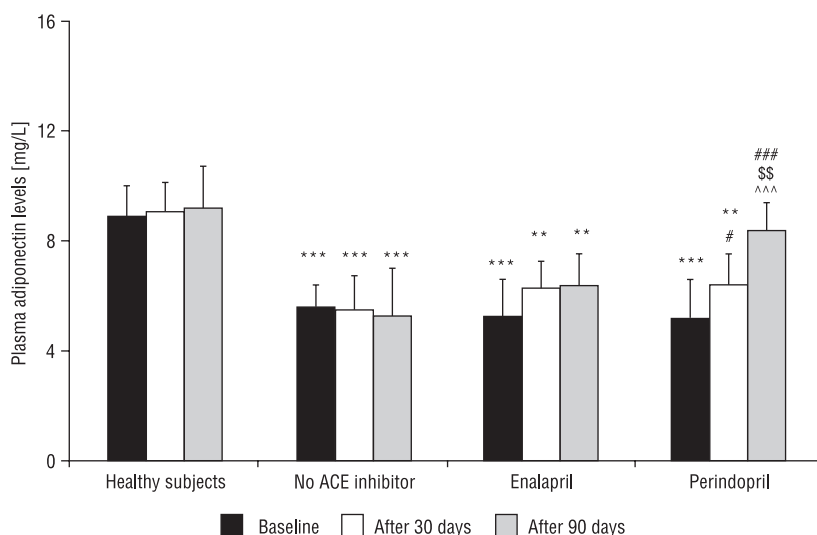


Figure 2. Effect of angiotensin-converting enzyme inhibitors on plasma adiponectin levels in normotensive patients with coronary artery disease. Data represent the mean \pm SD; $**p < 0.01$, $***p < 0.001$ v. healthy subjects; $\#p < 0.05$, $###p < 0.001$ v. pretreatment values; $^{ss}p < 0.01$ the effect 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 adiponektyny w osoczu pacjentów z chorobą niedokrwienną serca i prawidłową wartością ciśnienia tętniczego. Wyniki przedstawiają średnią \pm odchylenie standardowe; $**p < 0,01$, $***p < 0,001$ v. zdrowi ochotnicy; $\#p < 0,05$, $###p < 0,001$ v. wartość przed leczeniem; $^{ss}p < 0,01$ wpływ leku silniejszy niż po 30 dniach leczenia; $^{^^}p < 0,001$ pod koniec terapii wpływ perindoprilu silniejszy od enalaprilu

Discussion

The major finding of our study is that perindopril administered to normotensive CAD patients exhibited a stronger pleiotropic effect on the hormonal function of adipose tissue than enalapril, and that the drug-induced changes in plasma adipokines were not related to hypotensive or metabolic effects of ACE inhibitors.

We observed that CAD patients exhibited higher plasma levels of leptin as well as reduced plasma content of adiponectin, when compared with healthy controls. These results cannot be interpreted as a result of the presence of concomitant disorders known to affect adipokine production, as all subjects suffering from diabetes, obesity, arterial hypertension, and dyslipidaemia were excluded from the study. Therefore, differences between CAD individuals and healthy subjects seem to reflect the presence of atherosclerotic changes in the coronary vasculature. Taking into account that most included patients were treated with cardiovascular drugs, we cannot exclude that the difference may be even more pronounced in subjects with either untreated or insufficiently treated CAD. Interestingly, at baseline conditions plasma levels of leptin and adiponectin correlated with both systolic and diastolic blood pressure. This means that in subjects with concomitant presence of CAD and arterial hypertension, abnormalities

in adipokine release are probably more expressed than in individuals with only one of these disorders.

Both perindopril and enalapril treatment were well tolerated and resulted in only an insignificant reduction of both diastolic and systolic blood pressure. This indicates that, if administered at doses used in our study, ACE inhibitors do not increase the risk of excessive reduction in blood pressure and therefore may be safely used in CAD subjects without arterial hypertension.

To the best of our knowledge our study is the first one which assessed adipokine levels during treatment with more than one ACE inhibitor. This fact seems a little surprising taking into account the marked pharmacokinetic and pharmacodynamic differences between various ACE inhibitors. Some of these agents (perindopril, quinapril, and ramipril) exhibit a strong affinity for target tissues, while the others (captopril and enalapril) are characterized by relatively weak tissue affinity [31, 32]. The former group is often named tissue-type, while the latter is known as plasma-type ACE inhibitors. Our results, which showed much stronger action of perindopril than enalapril on plasma adipokine levels, indicate that pharmacokinetic and pharmacodynamic differences between various ACE inhibitors may determine the strength with which these agents affect adipokine release. This finding seems to be clinically relevant because both these adipose tissue prod-

ucts are directly involved in atherogenesis. Adiponectin exhibits a multidirectional anti-atherogenic action because it inhibits proliferation of smooth muscle cells, reduces macrophage cholesterol accumulation, prevents macrophage foam cell transformation, inhibits the endothelial expression of adhesive molecules, reduces proinflammatory cytokine release, and retards the development and progression of atherosclerotic lesions in atherosclerosis-prone mouse strains [24, 33]. The opposite action is produced by leptin, which enhances angiogenesis, stimulates oxidative stress in endothelial cells, increases vascular wall calcium content, and may induce proliferation and migration of smooth muscle cells [25, 34]. Taking into account the relationship between low adiponectinaemia and high leptinaemia and the risk of CAD and its complications [26–29], the obtained results indicate that tissue-type ACE inhibitors probably bring more benefits to subjects with isolated CAD than plasma-type ones. The observed differences between perindopril and enalapril may, in part, explain inter-study differences concerning ACE inhibitor action on plasma adipokines. Only an insignificant reduction in plasma leptin and a slight increase in plasma adiponectin are line with weak potency of enalapril to alter plasma levels of total or high molecular weight (HMW) adiponectin and HMW/total adiponectin ratio in CAD patients, observed recently by other authors [35].

Interestingly, perindopril-induced and, to a lesser extent, enalapril-induced increase in plasma adiponectin and a reduction in plasma leptin did not correlate with the insignificant reduction in blood arterial pressure. A similar hypotensive-independent effect of perindopril on leptinaemia was found recently in rats [36]. This indicates that the improvement in adipose tissue secretory function occurs irrespective of blood pressure and that it is present in individuals in whom ACE inhibitors produce no effect on arterial pressure. This finding is in line with our previous results [23]. Taking into account the inverse relationship between plasma adiponectin and the risk of CAD and the positive correlation between plasma leptin and the risk of CAD, our results may justify the routine use of ACE inhibitors in normotensive CAD patients.

Our study excluded not only subjects with arterial hypertension, but also individuals suffering from diabetes mellitus, obesity, and dyslipidaemia. Therefore, treatment-induced improvement in adipose tissue function cannot be explained by improvement in glucose and lipid metabolism and body weight.

It should be stressed that most patients included in this study had been, before the beginning of the treatment period, treated with acetylsalicylic acid, a statin, as well as with a β -adrenolytic agent. The fact that despite this, perindopril improved the hormonal function

of human adipose tissue, evidences the rationale of the use of this agent, and probably also other tissue-type ACE inhibitors in CAD patients, in whom clinically the disease is controlled by other drugs. The fact that perindopril-induced changes in plasma adipokines did not correlate with its action on plasma glucose and lipid profile indicates that this action does not result from metabolic effects of perindopril and that non-obese, normoglycaemic and normolipidaemic patients may benefit from this form of therapy.

The value of the obtained results may be limited by at least two reasons. Firstly, our study was a retrospective analysis of the stored samples. However, the original study was prospective in nature and patients were randomized to perindopril or enalapril. Secondly, the diagnosis of CAD was established indirectly on the basis of clinical manifestations and/or the results of the exercise test. Because no coronary angiography was performed, we cannot exclude that among the participants there were individuals misdiagnosed with CAD.

Conclusions

Our study has shown increased leptin and a reduced adiponectin plasma levels in normotensive CAD patients. Perindopril has been found to be more effective than enalapril, when it comes to affecting the hormonal function of human adipose tissue. This suggests that tissue-type ACE inhibitors appear to be a better treatment option for normotensive individuals with CAD than plasma-type ones.

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